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Seven Years of *Clinical Thyroidology*

This is the 21st issue of *Clinical Thyroidology* to be published in the seven years since the ATA acquired the journal and I became the editor in 2001. All the issues have looked like this one, with summaries and commentaries on 20 recently published original scientific articles, for a total of 420 articles from 117 journals. I have written the summaries and many of the commentaries, but many others have contributed commentaries as well. The articles have covered 22 topics in thyroidology, an obviously artificial subdivision of the discipline.

Currently, each new issue of the journal is mailed to all members of the ATA, and it is posted simultaneously at www.thyroid.org. Both members and nonmembers may sign up to receive email notification of electronic publication. The number of nonmember subscribers has increased progressively, and is currently approximately 2000 people from over 100 countries. It seems that *Clinical Thyroidology* is being seen by increasing numbers of people, always reassuring to an editor and hopefully of long-term benefit to the ATA.

Clinical Thyroidology has been a mostly one-person journal from the editorial perspective, but it could not have been published without help. That help has been provided by Ms. Kandra Files and Ms. Karen Durland, as layout and composition professionals tolerant of my repeated requests for revisions, Ms. Debbi Stone, an exceptional proofreader, and Ms. Bobbi Smith and her staff at the ATA office, as publisher of the journal.

This will be my last edition of the journal. I am grateful to the ATA for allowing me to serve for these seven years. It has been a wonderful learning experience, a fine opportunity to comment on many topics in thyroidology, some work, and great fun.

May the new editor find it to be the same.

Robert D. Utiger, M.D.

Most abnormalities of serum thyrotropin concentrations are transient

Meyerovitch J, Rotman-Pikielny P, Sherf M, Battat E, Surks MI. Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. Arch Intern Med 2007;167:1533-8.

SUMMARY

Background Subclinical thyroid disease, as defined by high or low serum thyrotropin (TSH) concentrations but normal serum free thyroxine (T_4) concentrations, is common in adults. This study was done to determine the frequency with which primary care physicians ordered measurements of serum TSH and the course of patients with subclinical thyroid disease who were not treated.

Methods The study group consisted of all patients 21 years of age and older enrolled in a medical plan in whom serum TSH was measured (reference range, 0.35 to 5.5 mU/L) in the course of outpatient care in 2002 and who were followed through 2006. Patients with known thyroid disease or previously abnormal serum TSH values were excluded, as were those treated with drugs that alter thyroid function and women who were pregnant during the study period.

Results Serum TSH was measured at least once in 422,242 patients (278,155 women and 144,087 men), 18 percent of those enrolled in the plan. The highest testing rates were in women and men aged 40 to 79 years (approximately 30 and 20 percent, respectively). Serum TSH values were abnormal in 21,003 patients (5.0 percent) (Table 1).

Table 1. Initial Serum TSH Concentrations in 422,242 Outpatients.

Serum TSH (mU/L)	Women	Men	Total
Normal	262,071 (62%)	139,168 (33%)	401,239 (95%)
>10	2,348 (0.5%)	715 (0.2%)	3,063 (0.7%)
>5.5 to ≤10	9,991 (2.4%)	2,824 (0.7%)	12,815 (3.0%)
<0.35	3,745 (0.9%)	1,380 (0.3%)	5,125 (1.2%)

Serum free T_4 was measured in 18,693 of the 21,003 patients (89 percent) who had abnormal serum TSH values. Among them, serum free T_4 values were normal in 70 percent of those with serum TSH values >10 mU/L and 93 percent of those with values >5.5 to 10 mU/L, indicative of subclinical hypothyroidism. Ninety-one percent of those with serum TSH values <0.35 mU/L had normal serum free T_4 values, indicative of subclinical hyperthyroidism.

During the 5-year study period, 15,081 patients (4 percent) were treated for hypothyroidism or hyperthyroidism after one or more serum TSH measurements. Among the remaining 407,161 patients, serum TSH was measured only once in 60,612 (15 percent) and two or more times in 346,549 (85 percent) (Table 2). The mean interval between the first and second tests was 19 months.

Table 2. Results of Second Serum TSH Measurements in 346,549 Outpatients.

Second Serum TSH (mU/L)	First Serum TSH (mU/L)			
	Normal (n=334,572)	>10 (n=669)	>5.5 to ≤ 10 (n=7,533)	<0.35 (n=3,775)
Normal	98%	28%	62%	52%
>10 mU/L	0.1%	35%	2.9%	0.6%
>5.5 to 10 mU/L	1.4%	36%	35%	1.2%
<0.35 mU/L	0.6%	0.4%	0.3%	47%

Percentages do not add to 100 because of rounding.

Nearly all patients with normal values when first tested had normal second values (Table 2), as did many whose first value was abnormal. Among the patients whose first serum TSH value was >5.5 to ≤10 mU/L, only 2.9 percent had second values >10 mU/L.

Conclusion Among outpatients aged 21 years and older, the frequency of abnormal serum TSH concentrations is low. When tested again, the second value is normal in nearly all patients whose first value was normal and in most untreated patients whose first value was abnormal.

COMMENTARY

Both subclinical hypothyroidism and subclinical hyperthyroidism may have long-term adverse effects. However, no clear benefit of treatment of patients with either has yet been documented. Determining benefit will require that the two entities be very clearly defined and that their untreated natural history be determined at the same time. This study demonstrates that both disorders are often transient, so that starting a treatment study without documenting persistence of both abnormal serum TSH and normal serum free T_4 concentrations would be inappropriate. It is equally important that there be very precise definitions of subclinical hypothyroidism and subclinical hyperthyroidism. For example, should subclinical hyperthyroidism be defined as a serum TSH concentration less than the lower limit of the reference range (<0.35 mU/L in this study) or <0.1 mU/L, as in some other studies.

This study confirms that progression of subclinical hypothyroidism relates to the initial serum TSH value, in that the frequency of follow-up serum TSH values >10 mU/L was higher in patients whose initial value was >5.5 to ≤10 mU/L than in those whose initial value was normal. With such a large cohort, the inverse analysis for subclinical hyperthyroidism should be feasible. Would the frequency of progression of subclinical hyperthyroidism be higher in patients with initial values of 0.1 to 0.34 mU/L or those with normal initial values? Conversely, would the frequency of regression to normal values be higher in those with initial values of 0.1 to 0.34 mU/L or those with initial values <0.1 mU/L?

Notwithstanding the abundant follow-up results, quantitative conclusions from this retrospective study may be inaccurate because approximately 3,700 patients with abnormal initial serum TSH concentrations were treated and therefore excluded from follow-up. If they were more severely affected, based on symptoms, presence of goiter, or degree of serum TSH or free T_4 abnormality, the analysis may underestimate the likelihood of abnormality at follow-up.

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Smoking stimulates thyroid secretion

Asvold BO, Bjøro T, Nilsen TI, Vatten LJ. Tobacco smoking and thyroid function: a population-based study. Arch Intern Med 2007;167:1428-32.

SUMMARY

Background Smoking seems to stimulate thyroid hormone secretion, in addition to being a risk factor for Graves' hyperthyroidism and ophthalmopathy. This study was done to determine the relationships between smoking and pituitary–thyroid function in a large number of subjects.

Methods The study group consisted of 30,834 subjects (20,479 women, 10,355 men) aged 20 years or older living in one county in Norway. They were selected from a larger cohort of 66,140 subjects who enrolled in the county-wide Nord-Trøndelag Health Study between 1995 and 1997 because they had no history of thyroid disease and at enrollment had provided information about smoking, including the age at which they had started smoking, the number of years they had smoked, the number of cigarettes smoked daily, and if and when they had stopped smoking. Serum thyrotropin (TSH) was measured in all women and in 50 percent of men older than 40 years and in 5 percent of women and men aged 20 to 40 years. Serum free thyroxine (T_4) was measured in subjects whose serum TSH concentration was >4.0 mU/L or <0.2 mU/L.

Results The geometric mean serum TSH concentrations in both women and men were highest in those who had never smoked and lowest in the current smokers (Table 1).

Table 1. Geometric Mean Serum TSH Concentrations in 30,834 Never Smokers, Former Smokers, and Current Smokers.

Women	No.	Serum TSH (mU/L)
Never smokers	10,622	1.66
Former smokers	4,240	1.61
Current smokers	5,577	1.33
Men		
Never smokers	3,295	1.70
Former smokers	4,037	1.61
Current smokers	3,023	1.40

Among those who had stopped smoking, serum TSH concentrations increased gradually with time after cessation of smoking, especially in women.

Among current smokers, serum TSH concentrations were lower in those who smoked more often. For example, among the women, the mean serum TSH concentrations were 1.61 mU/L in the never smokers, and approximately 1.30 mU/L in those who smoked 13 to 17 and ≥18 cigarettes daily. The results were similar among the men.

Among the women, the frequency of overt and subclinical hypothyroidism was higher in the never smokers than in the current smokers (Table 2). The results were similar among the men, although fewer men had high serum TSH concentrations. Conversely, overt and subclinical hyperthyroidism were more frequent in the women who were current smokers than in those who had never smoked (few men had low serum TSH concentrations).

Table 2. Frequency of Overt and Subclinical Hypothyroidism and Hyperthyroidism among Women in Relation to Smoking Status and Cessation of Smoking.

Smoking status	Overt Hypo-thyroidism*	Subclinical Hypo-thyroidism*	Overt Hyper-thyroidism**	Subclinical Hyper-thyroidism**
Never (n=10,662)	89 (0.8%)	620 (5.8%)	32 (0.3%)	44 (0.4%)
Current (n=5,577)	25 (0.4%)	157 (2.8%)	28 (0.5%)	29 (0.5%)

*Serum TSH >4.0 mU/L, serum free T_4 low or normal.
**Serum TSH <0.2 mU/L, serum free T_4 high or normal.

Conclusion Smoking stimulates thyroid secretion, so that smokers have lower serum TSH concentrations and a lower prevalence of subclinical and overt hypothyroidism, as compared with nonsmokers, and among women a higher prevalence of overt and subclinical hyperthyroidism.

COMMENTARY

Smoking has diverse effects on thyroid function. The most common effect is the TSH-like effect described by Asvold et al. and in other cohorts in Europe and the United States (1). As compared with nonsmokers, smokers have lower serum TSH concentrations, and they tend to have higher serum T_4 concentrations. In addition, there is a dose response—more smoking, lower serum TSH values—and a cessation-related response—longer cessation of smoking, higher serum TSH values. Smokers also have larger thyroid glands and higher serum thyroglobulin values. Finally, the prevalence of overt and subclinical hyperthyroidism is higher and that of subclinical and overt hypothyroidism is lower in smokers.

Why is the thyroid stimulated in smokers? The one factor derived from smoking known to alter thyroid function is thiocyanate, which has antithyroid activity. One possible smoking-related thyroid stimulator is nicotinergic activation of the thyroid, but if so, why doesn't it wane soon after cessation of smoking? Another possibility is that smoking leads to the production of a very low level of TSH receptor–stimulating antibodies, equivalent to the effect of, for example, 0.2 to 0.5 mU/L of TSH. Smoking is a modest risk factor (two-fold increase in risk) for Graves' hyperthyroidism. Perhaps this effect of smoking to increase susceptibility to Graves' hyperthyroidism, however mediated, is widespread, but much weaker, in many people.

Robert D. Utiger, M.D.

Reference

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Cardiac abnormalities may be the dominant manifestations of thyroid storm in young men

Ngo SY, Chew HC. When the storm passes unnoticed—a case series of thyroid storm. Resuscitation 2007;73:485-90.

SUMMARY

Background The clinical spectrum of hyperthyroidism is broad, varying from no symptoms or signs to severe, life-threatening hyperthyroidism. This report describes three patients considered to have thyroid storm in whom the illness was dominated by cardiac symptoms and signs.

Case 1 A 32-year-old man came to an emergency room with a one-week history of dyspnea, edema, tremor, and heat intolerance. Physical examination revealed atrial flutter (134 ventricular beats/min), normal blood pressure (103/58 mm Hg) and pulse oximetry, proptosis, diffuse goiter, and edema. Electrocardiography (ECG) showed atrial flutter, and chest x-ray cardiomegaly and mild pulmonary congestion. He was hospitalized and treated with propranolol.

Four hours later, he had chest discomfort and became breathless, with severe hypotension, continued tachycardia, tachypnea, diaphoresis, and flushing. Repeat chest x-ray showed severe pulmonary congestion, and echocardiography mitral and tricuspid regurgitation and a left ventricular ejection fraction (LVEF) of 25 percent. His serum free T_4, free T_3, and TSH values are shown in the Table. He was treated for hyperthyroidism and congestive heart failure. He improved and was discharged nine days after admission.

Case 2 A 28-year-old man presented with a one-week history of dyspnea, orthopnea, and anasarca. Physical examination revealed tachycardia (170 beats/min), normal blood pressure (103/73 mm Hg) and pulse oximetry, jugular venous distention, pulmonary congestion, and scrotal and leg edema. ECG showed atrial fibrillation, and chest x-ray cardiomegaly, pulmonary congestion, and a right pleural effusion. He was hospitalized and treated with diltiazem, digoxin, and propranolol. He had recurrent atrial fibrillation, became hypotensive, and collapsed. An intraaortic balloon pump was inserted, and he was treated with carvedilol, amiodarone, and an antithyroid drug. Echocardiography showed dilated cardiomyopathy and a LVEF of 20 percent. The results of thyroid tests are shown in the Table. He remained very ill, and died on the ninth hospital day.

Table. Initial Serum Thyroid Hormone and TSH Concentrations in Three Patients with Thyroid Storm.

	Serum Free T_4 (ng/dl)	Serum Free T_3 (ng/dl)	Serum TSH (mU/L)
Patient 1	6.9	2.0	<0.006
Patient 2	4.5	—	<0.006
Patient 3	>7.0	>2.3	<0.01
Reference range	0.7-1.5	0.3-0.6	—

To convert serum free T_4 and free T_3 values to pmol/L, multiply by 12.9 and 15.4, respectively.

Case 3 A 30-year-old man was hospitalized for evaluation of fever and shortness of breath of two day's duration. He had anorexia, weight loss, diarrhea, and heat intolerance for two months. He had hyperthyroidism 10 years earlier, and had taken an antithyroid drug until seven months earlier. Physical examination revealed a sick-appearing, anxious man with tachycardia (143 beats/min), blood pressure of 143/86 mm Hg, normal pulse oximetry, proptosis, diffuse goiter, pulmonary congestion, and edema. ECG showed supraventricular tachycardia, chest x-ray cardiomegaly and bilateral pleural effusions, and echocardiography left ventricular dilation and a LVEF of 30 percent. He was treated with furosemide, digoxin, carbimazole, hydrocortisone, and antibiotics. He improved rapidly and was discharged six days later.

Conclusion Cardiac arrhythmias and contractile dysfunction may be the major manifestations of thyroid storm in young patients.

COMMENTARY

The term thyroid storm is applied to patients who have severe clinical manifestations of hyperthyroidism, including marked cardiac dysfunction (tachycardia, atrial fibrillation, congestive heart failure), changes in mental function (agitation, delirium, seizures, coma), gastrointestinal and hepatic dysfunction (abdominal pain, diarrhea, jaundice), and fever. There are no unique clinical, physiologic, or biochemical findings that define thyroid storm. Instead, it is a constellation of these symptoms and signs of such severity that they are life threatening. The rating system of Burch and Wartofsky (1), consisting of a point system based on gradations of temperature dysregulation, central nervous system changes, gastrointestinal and hepatic dysfunction, and cardiovascular dysfunction (range of possible scores, 10 to 140 points; a score of ≥45 points indicates thyroid storm and a score of 25 to 44 impending storm) provides some guidance in assessing severity. These are of course arbitrary gradations, but assessment using this system can help guide decisions about treatment, particularly its intensity.

Using this rating system, the three patients described by Ngo and Chew had thyroid storm. Their article emphasizes the importance of clinical recognition of thyroid storm and initiating early treatment. Unfortunately, little is said about the antithyroid and supportive therapy that was given. Typically, patients with thyroid storm are treated with high doses of methimazole or propylthiouracil, potassium iodide, glucocorticoids, and appropriate systemic support. The onset of action of iodide is rapid (hours), whereas that of the antithyroid drugs is slower (days). The role of β-adrenergic antagonist drugs is less clear, given the benefit of treating tachycardia versus the risk of impairing myocardial contractility. It seems preferable to avoid their use in patients with hyperthyroidism and acute cardiac decompensation unless there are other indications and the patients are carefully monitored.

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Reference

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Major cardiac events are common during follow-up in patients with amiodarone-associated hyperthyroidism

Conen D, Melly L, Kaufmann C, Bilz S, Ammann P, Schaer B, Sticherling C, Muller B, Osswald S. Amiodarone-induced thyrotoxicosis. Clinical course and predictors of outcome. J Am Coll Cardiol 2007;49:2350-5.

SUMMARY

Background Hyperthyroidism is a well-known adverse effect of the iodine-rich antiarrhythmia drug amiodarone. It takes two forms—iodine-induced hyperthyroidism and thyroiditis-induced hyperthyroidism. In this retrospective study, the long-term outcome of patients with amiodarone-associated hyperthyroidism was determined.

Methods The study subjects were 84 patients (22 women, 62 men; mean age, 60 years) treated with amiodarone between 1996 and 2005. The most common indications for amiodarone therapy were atrial fibrillation (48 patients [57 percent]) and ventricular tachycardia (27 patients [32 percent]). Twenty-five patients (30 percent) had coronary heart disease, 12 (14 percent) myocardial infarction, 6 (7 percent) myocarditis, and 3 (4 percent) congenital heart disease. Fifteen patients had iodine-induced hyperthyroidism and 69 thyroiditis-induced hyperthyroidism.

The patients' medical records were reviewed and surviving patients were interviewed. Particular attention was given to the patients' symptoms, signs, and left ventricular function, as determined by echocardiography, at the time of diagnosis of hyperthyroidism; and major cardiac events (myocardial infarction, heart failure, arrhythmia, stroke) and death after diagnosis and treatment of hyperthyroidism.

Results The mean duration of amiodarone therapy at the time of diagnosis of hyperthyroidism was 31 months (range, 19 to 38). The most common symptoms were weight loss (50 percent), increased perspiration (42 percent), palpitations (37 percent), hyperactivity (29 percent), and muscle weakness (27 percent). The left ventricular ejection fraction at that time was ≥50 percent in 57 patients (69 percent) and <50 percent in 26 (31 percent). Their mean serum free thyroxine (T_4) and thyrotropin (TSH) concentrations were 3.4 ng/dl (44 pmol/L) and 0.006 mU/L, respectively.

Most patients were treated with an antithyroid drug, prednisone (mean dose, 30 mg daily), or both (Table 1).

Table 1. Antithyroid Treatment of 84 Patients with Amiodarone-Associated Hyperthyroidism.

Antithyroid drug therapy	70 (83%)
Carbimazole	64 (76%)
Propylthiouracil	11 (13%)
Both*	5 (6%)
Prednisone	27 (32%)
Thyroidectomy	8 (10%)

*Changed from carbimazole to propylthiouracil because of agranulocytosis (4 patients) or hepatic dysfunction (1 patient).

The median times to normalization of serum free T_4 and TSH concentrations were 98 and 138 days, respectively, in the prednisone-treated patients and 108 and 141 days, respectively, in the antithyroid drug–treated patients. The 8 patients who underwent thyroid surgery were treated with an antithyroid drug for 112 days before the operation.

The median duration of follow-up after diagnosis of hyperthyroidism was 50 months, during which 16 patients (19 percent) died and 47 (56 percent) had major cardiac events. The mortality rate was similar in the patients with a normal left ventricular ejection fraction and those with a low ejection fraction, but the frequency of major cardiac events was higher in the patients with a low ejection fraction. Overall event-free survival was similar in these two groups, and it was lower in the patients treated with prednisone than in those not so treated.

Conclusion Amiodarone-associated hyperthyroidism usually occurs several years after initiation of the drug. The response to antithyroid drug or prednisone therapy is slow, and the long-term rates of major cardiac events and death are substantial.

COMMENTARY

Clinically important thyroid dysfunction occurs in up to 20 percent of patients treated with amiodarone, and it is probably the most common cause of drug-induced thyroid dysfunction. Many of the patients have thyroiditis-induced hyperthyroidism, but others have iodine-induced hyperthyroidism or iodine-induced hypothyroidism. The onset of hyperthyroidism may be delayed, and therefore thyroid function should be assessed periodically for as long as patients are treated with amiodarone and for several months thereafter, because of the very slow clearance of the drug.

Most of the patients in this study were thought to have thyroiditis-induced hyperthyroidism. However, the criteria used to distinguish the two types of hyperthyroidism (thyroid enlargement, findings on gray-scale and Doppler ultrasonography) are not very reliable, and some patients have features of both types.

The response to therapy was slow in the two main treatment groups in this study, and the improvement in some patients may have been spontaneous rather than due to antithyroid-drug or prednisone therapy, especially since amiodarone was discontinued in all patients. In patients with iodine-induced hyperthyroidism, the iodine pool should diminish with time, to the point at which intracellular iodine concentrations would be too low to sustain excess thyroid hormone production. And in those with thyroiditis-induced hyperthyroidism, the stores of thyroid hormone in the gland should be exhausted in weeks, and are unlikely to be replenished as long as the thyroiditis persists and TSH secretion is inhibited.

The long-term rates of cardiac events and death were high in these patients, but perhaps no higher than they would be in amiodarone-treated patients who had never had hyperthyroidism.

Robert D. Utiger, M.D.

Propylthiouracil can cause vasculitis and renal disease

Yu F, Chen M, Gao Y, Wang SX, Zou WZ, Zhao MH, Wang HY. Clinical and pathological features of renal involvement in propylthiouracil-associated ANCA-positive vasculitis. Am J Kidney Dis 2007;49:606-14.

SUMMARY

Background Patients with hyperthyroidism who are treated with an antithyroid drug, especially propylthiouracil (PTU), may have vasculitis associated with serum antineutrophil cytoplasmic antibodies (ANCA), and the vasculitis may involve the kidneys. In this study, the clinical features and course of patients with PTU-associated ANCA-positive vasculitis and renal disease were determined.

Methods Between 1999 and 2005, 19 patients with ANCA-positive vasculitis associated with PTU therapy were seen at one hospital in China, of whom 15 (13 women, 2 men; mean age, 26 years [range, 11 to 57]) had renal disease. All had been treated with PTU for hyperthyroidism caused by Graves' disease for 1.5 to 96 months (mean, 43).

The diagnosis of ANCA-positive vasculitis was based on nonspecific symptoms and signs of vasculitis, not specified, but presumably including fever and arthralgia; a positive serum test for ANCA, as detected by perinuclear immunostaining of neutrophils; and exclusion of other disorders, such as systemic lupus and hepatitis B and C infection. Renal disease was defined as the presence of hematuria or proteinuria. All 15 patients underwent renal biopsy. Treatment consisted of cessation of PTU therapy in all patients, and oral or intravenous glucocorticoids, cyclophosphamide, mycophenolate mofetil, or plasmapheresis in 13 (87 percent).

Results Four of the 15 patients (27 percent) with PTU-associated ANCA-positive vasculitis and renal disease presented with gross hematuria, and the remainder had microscopic hematuria. One patient presented with the nephrotic syndrome, 5 with rapidly progressive glomerulonephritis, and 1 with oliguria. All had proteinuria (mean, 1.2 g/24 hours). Their mean serum creatinine concentration was 2.6 mg/dl (230 μmol/L) and their mean estimated glomerular filtration rate was 62 ml/minute (range, 3 to 92). Thirteen patients (87 percent) had nonspecific symptoms of vasculitis, 9 (60 percent) skin involvement, and 8 (53 percent) pulmonary involvement. Twelve patients (80 percent) were anemic, 13 (87 percent) had a high erythrocyte sedimentation rate, and 11 (73 percent) had a high serum C-reactive protein concentration.

The ANCA included antibodies specific for myeloperoxidase in all 15 patients, and antibodies specific for cathepsin, leukocyte elastase, azurocidin, and proteinase-3 in some of them. No patient had cytoplasmic ANCA.

The renal biopsies revealed necrotizing crescentic glomerulonephritis in 10 patients (67 percent), IgA nephropathy in 2 (13 percent), and minimal involvement in 3 (20 percent). Seven of the 10 patients (70 percent) with necrotizing crescentic glomerulonephritis had glomerular deposition of immune complexes.

Thirteen patients (87 percent) were treated with oral prednisone, 7 (47 percent) with intravenous methylprednisolone, 9 (60 percent) with cyclophosphamide, 2 (13 percent) with plasmapheresis, and 1 (7 percent) with mycophenolate mofetil. After three months, all patients had improved, and 11 (73 percent) had complete remission of vasculitis and renal disease.

Conclusion Serum ANCA, vasculitis, and renal disease, manifested by hematuria, proteinuria, and mainly necrotizing crescentic glowerulonephritis, may occur in patients with hyperthyroidism who are treated with PTU.

COMMENTARY

A few patients with Graves' hyperthyroidism have serum ANCA before any treatment, and ANCA can be detected in considerably more patients during antithyroid drug treatment, especially among those treated with PTU. For example, in a study of 320 patients, serum ANCA were present in 4 percent of untreated patients, 33 percent of patients treated with PTU, and 16 percent of patients treated with carbimazole (1). In another study of 119 patients the respective percentages were 0, 38, and 0 (2). The antibodies usually appear after many months of treatment (43 months in this study) and disappear slowly after the drugs are stopped. Most of the patients have been euthyroid when found to have serum ANCA, most likely a reflection of prolonged antithyroid drug treatment.

Of clinical importance, many of the patients found to have serum ANCA never have vasculitis, and among those who have vasculitis not all have renal disease. Whatever the clinical manifestations of vasculitis, nearly all patients have improved after the antithyroid drug was stopped, with or without glucocorticoid or other therapy.

Should serum ANCA be measured periodically in patients receiving long-term antithyroid drug therapy, or only in patients who have any symptoms of vasculitis? If serum ANCA are found, and there are manifestations of vasculitis, the drug should be stopped. But what if there are no manifestations of vasculitis?

Robert D. Utiger, M.D.

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Recurrent hyperthyroidism after antithyroid drug therapy is common in patients with severe Graves' ophthalmopathy

Eckstein AK, Lax H, Losch C, Glowacka D, Plicht M, Mann K, Esser J, Morgenthaler NG. Patients with severe Graves' ophthalmopathy have a higher risk of relapsing hyperthyroidism and are unlikely to remain in remission. Clin Endocrinol (Oxf) 2007;67:607-12.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease have ophthalmopathy, generally thought to indicate of more severe Graves' disease. This study was done to determine the effect of varying degrees of ophthalmopathy and other factors on the natural history of Graves' hyperthyroidism.

Methods The study subjects were 158 patients with Graves' hyperthyroidism and ophthalmopathy. The inclusion criteria were onset of ophthalmopathy within the preceding six months, antithyroid drug therapy for hyperthyroidism for at least one year, and follow-up for at least 18 months. Hyperthyroidism was considered in remission if the patient remained euthyroid for one year after cessation of antithyroid drug therapy. Patients who had recurrent hyperthyroidism were treated with an antithyroid drug, radioiodine, or thyroidectomy.

The patients were examined at three-month intervals until the ophthalmopathy was stable for at least six months or an operation was done to reverse ocular pathology. The activity of ophthalmopathy was assessed using the Clinical Activity Score, a 10-point score based on eye erythema, redness, swelling, and impaired function (0, inactive; 10, active), and its severity was assessed using the NOSPECS score (0, no signs; 16, marked signs). Serum thyrotropin (TSH)-receptor antibodies (TSHR-Ab) were measured by receptor assay (normal, <1.0 IU/L). Patients who had Clinical Activity Scores >2 were offered oral or intravenous glucocorticoid therapy, and those who had decreased ocular motility or increased activity after glucocorticoid therapy were offered orbital radiation therapy.

Eleven to 14 months after the onset of ophthalmopathy the patients were subdivided according to their course to date: mild course, CAS<4 and NOSPECS score <5, and severe course, CAS ≥4 and NOSPECS score ≥5.

Results The onset of ophthalmopathy preceded the onset of hyperthyroidism in 11 patients (7 percent), was at the same time in 79 (50 percent), was later in 38 (24 percent), and was after recurrence of hyperthyroidism and destructive therapy in 30 (19 percent).

The course of ophthalmopathy was mild in 65 patients (41 percent) and severe in 93 (59 percent). The median follow-up after diagnosis of hyperthyroidism and onset of symptoms of ophthalmopathy in the two groups was similar (46 vs. 41 months and 35 vs. 36 months, respectively). There were differences in these two groups in age, smoking status, and treatment of ophthalmopathy (Table).

Table. Characteristics of Patients with Ophthalmopathy (Mild Course vs. Severe Course).

	Mild Course (n=65)	Severe Course (n=93)
Women/men	60/5	80/13
Age (median – yr)	47	53
Smokers	32 (49%)	67 (72%)
Glucocorticoid therapy	49 (75%)	88 (95%)
Orbital radiation	20 (31%)	88 (95%)
One-year remission of hyperthyroidism	27 (42%)	7 (8%)
Recurrent hyperthyroidism	38 (58%)	86 (92%)

After one year of antithyroid drug therapy, 27 mild-course patients (42 percent) remained euthyroid for at least one year, as compared with 7 (8 percent) in the severe-course group.

Serum TSHR-Ab values in the mild-course and severe-course groups six months after the onset of ophthalmopathy were 2.2 and 15.6 IU/L, respectively, and they were 1.3 and 6.3 IU/L, respectively, after antithyroid drug therapy for one year. High serum TSHR-Ab values at this time were highly predictive of recurrent hyperthyroidism. Age, sex, and smoking status were not associated with recurrent hyperthyroidism.

Conclusion Patients with severe Graves' ophthalmopathy or high serum TSHR-Ab concentrations after antithyroid drug therapy for one year are likely to have recurrent hyperthyroidism.

COMMENTARY

The manifestations of Graves' disease are, in decreasing order of frequency, hyperthyroidism, goiter, ophthalmopathy, localized myxedema, and thyroid acropachy. The two less common manifestations of the disorder virtually always occur in patients who have long had thyroid disease and ophthalmopathy. Patients with hyperthyroidism and goiter have high serum TSHR-Ab concentrations, which in the context of these clinical features of the disease may be taken to be stimulating antibodies. Serum TSHR-Ab concentrations are higher in patients with the extrathyroidal manifestations of the disease, probably as an indicator of the severity of the disease, but there is little evidence that they cause them.

Eckstein et al. found that the severity of ophthalmopathy, the likelihood of recurrent (or persistent) hyperthyroidism, and high serum TSHR-Ab concentrations were interrelated. Recurrent hyperthyroidism isn't necessarily severe hyperthyroidism, but it does indicate that the Graves' disease is persistent. And if it is persistent, ophthalmopathy is more likely to occur or worsen. Furthermore, ophthalmopathy may be exacerbated by the fluctuations of thyroid secretion that are likely to occur during recurrence of hyperthyroidism and during and after treatment of recurrent hyperthyroidism. There is no direct way to ameliorate the severity of Graves' disease, but the severity of ophthalmopathy can be at least minimized by avoiding fluctuations in thyroid secretion.

Robert D. Utiger, M.D.

Hypopituitarism may follow traumatic brain injury and aneurysmal hemorrhage

Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A. Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA 2007;298:1429-38.

SUMMARY

Background Hypopituitarism can occur after traumatic brain injury or subarachnoid hemorrhage from a cerebral-artery aneurysm, but it may be difficult to identify because of neurologic and psychiatric dysfunction. In this study, the frequency and time of onset of hypopituitarism after traumatic brain injury and aneurysmal subarachnoid hemorrhage were summarized from the literature.

Methods Nineteen studies describing the results of evaluation of hypothalamic–pituitary function in 1137 patients (74 children, 1063 adults) with traumatic brain injury (14 studies, 1015 patients) or aneurysmal subarachnoid hemorrhage (5 studies, 122 patients) were identified. The studies were cross-sectional, but six had a longitudinal component. The patients in the trauma group had scores on the Glasgow Coma Scale (GCS, based on assessment of eye-opening, verbal, and motor responses) ranging from ≤8 (severe injury) to ≤13 (moderate injury). The spectrum of neurologic deficit in the hemorrhage group ranged from none to deep coma.

Many studies were done 3 to 36 months after the acute event, but the range was 1 month to 22 years. Corticotropin (ACTH), gonadotropin (follicle-stimulating hormone/luteinizing hormone [FSH/LH]), and thyrotropin (TSH) deficiency were defined on the basis of clinical manifestations and basal hormone measurements, with the addition of the results of ACTH-stimulation tests in 6 studies. Growth hormone (GH) secretion was assessed by provocative tests in 17 studies.

Results The frequency of one or more anterior pituitary hormone deficiencies five or more months after the acute event varied from 4 to 12 percent in the trauma group and 6 to 20 percent in the hemorrhage group (Table 1). Among the deficiencies, growth hormone deficiency was the most common and central hypothyroidism the least common. The pooled prevalence of any deficiency was 28 percent in the trauma group and 47 percent in the hemorrhage group.

Table 1. Frequency of Anterior Pituitary Hormone Deficiencies Five or More Months after Traumatic Brain Injury or Aneurysmal Subarachnoid Hemorrhage.

	Trauma Group (n=809)	Hemorrhage Group (n=102)
ACTH deficiency	66 (8%)	21 (20%)
FSH/LH deficiency	101 (12%)	6 (6%)
GH deficiency	100 (12%)	26 (25%)
TSH deficiency	33 (4%)	6 (6%)
Multiple deficiencies	60 (8%)	9 (9%)

The frequency of one or more anterior pituitary hormone deficiencies was higher in the patients with severe brain injury (GCS score <8) than in those with less severe injury, but there was no correlation between hypopituitarism and severity of coma in the hemorrhage group.

Among the patients tested during the acute phase or at three months and then again at 12 months, the major change was a decrease in the frequency of gonadotropin deficiency (Table 2). At 12 months, 113 patients no longer had one previously present deficiency and 50 patients had a new deficiency.

Table 2. Frequency of Anterior Pituitary Hormone Deficiencies at Different Times after Traumatic Brain Injury and Aneurysmal Subacrachnoid Hemorrhage.

	Acute Phase (n=102)	3 Months (n=148)	12 Months (n=240)
ACTH deficiency	13 (13%)	21 (14%)	6 (12%)
FSH/LH deficiency	60 (59%)	36 (24%)	32 (13%)
GH deficiency	19 (19%)	23 (16%)	43 (18%)
TSH deficiency	4 (4%)	10 (7%)	10 (4%)
Multiple deficiencies	9 (17%)	16 (11%)	15 (6%)

Conclusion One or more anterior pituitary hormone deficiencies may occur after traumatic brain injury or aneurysmal subarachnoid hemorrhage. The deficiencies may be transient or permanent, and their onset acute or delayed.

COMMENTARY

Postmortem examination in patients with traumatic head injury or subarachnoid hemorrhage often reveals infarcts, necrosis, or hemorrhagic lesions in the hypothalamus or pituitary gland, so it is not surprising that they have abnormal pituitary hormone secretion (including hyperprolactinemia and vasopressin deficiency, not considered here). However, the clinical importance of the deficiencies described in this summary review is not known, assuming that the patients indeed have deficiencies, and not simply slightly low serum concentrations of hormones whose secretion is pulsatile, such as LH; decreases in the serum concentrations of transport proteins, such as cortisol-binding globulin; or subnormal responses to pharmacologic stimuli that are of little physiologic importance.

Some of the deficiencies found in the acute phase of illness in these patients, for example, growth hormone, FSH/LH, or TSH deficiency, also occur in patients with other acute illnesses, and treatment is not usually considered beneficial. Other acute deficiencies may be due to the high doses of glucocorticoids or drugs given at that time. Persistent deficiencies or deficiencies identified after the acute phase may well be more important. They could contribute to prolonged or poor recovery, but their clinical importance and the benefits of treatment have not been studied. There is probably no one optimal time to assess pituitary function after head injury or subarachnoid hemorrhage, but it ought to be done at least once and preferably twice.

Robert D. Utiger, M.D.

Thyroxine treatment is not beneficial in patients with subclinical hypothyroidism

Villar HC, Saconato H, Valente O, Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev 2007;(3):CD003419.

SUMMARY

Background Subclinical hypothyroidism (high serum thyrotropin [TSH] and normal serum free thyroxine [T_4] concentrations) is common, but whether treatment is beneficial is controversial. This pooled analysis of studies of T_4 treatment in patients with subclinical hypothyroidism was undertaken to determine the efficacy of T_4 treatment in these patients.

Methods Multiple databases of published articles (MEDLINE, EMBASE), clinical trials databases, and reference lists were searched to identify randomized controlled studies in which the effects of T_4 or placebo were compared in patients with subclinical hypothyroidism.

The primary outcomes were the effects of T_4 treatment and placebo on cardiovascular morbidity and mortality, symptoms of hypothyroidism, and quality of life (including cognitive and emotional function). The secondary outcomes were changes in serum lipid concentrations, cardiac function, and bone mineral density. Changes in serum TSH concentrations and adverse effects of treatment (symptoms of hyperthyroidism) also were evaluated.

Results Twelve studies meeting the inclusion criteria were identified. They included 350 patients, mostly adult women; their mean age was 35 years in nine studies, and all were >50 years old in the other three studies. Seven studies included patients known to have thyroid disease, whereas in five studies no patient had a history of thyroid disease. Most patients had serum TSH concentrations <15 mU/L (highest, 55 mU/L). The dose of T_4 was titrated to reduce serum TSH concentrations to within the normal range in most studies; the mean final doses ranged from 65 to 150 μg daily. The duration of the studies ranged from 6 to 14 months. No patient dropped out in five studies and <10 percent dropped out in four other studies.

Serum TSH concentrations were lower at the end of T_4 treatment, as compared with placebo, in all nine studies (335 patients) in which the results were reported.

Cardiovascular morbidity or mortality was not analyzed in any study. The results of analyses of the other primary outcomes and the secondary outcomes are shown in the Table.

Table. Results of T_4 Treatment or Placebo in Patients with Subclinical Hypothyroidism.

Outcome	Studies (no.)	Patients (no.)	Studies with Benefit of T_4 Treatment (no.)	Pooled Benefit of T_4 Treatment*
Symptoms of hypothyroidism	7	289	1	No
Quality of life	3	200	1**	No
Serum cholesterol	6	255	1	Yes
Serum LDL cholesterol	4	188	1	No
Serum HDL cholesterol	4	188	0	No
Serum triglycerides	5	221	0	No
Cardiac function	4	132	6**	NA†
Bone mineral density (L2–L4)	2	47	0	No

*Weighted relative risk or weighted mean response favoring T_4 treatment.
**Results of multiple tests in several of the quality-of-life and cardiac-function studies.
†Not analyzed.

Adverse effects, reported in four studies (138 patients), were not different in the T_4-treatment and placebo groups.

Conclusion Symptoms of hypothyroidism, quality of life, serum lipid concentrations, and cardiac function do not change more in response to T_4 treatment, as compared with placebo, in patients with subclinical hypothyroidism.

COMMENTARY

Whether patients with subclinical hypothyroidism should be treated with T_4 is controversial. A 2004 review found insufficient evidence to support the hypothesis that T_4 treatment improved symptoms, serum cholesterol concentrations, or cardiac function in these patients (1). Nonetheless, many physicians treat patients whose serum TSH concentrations are higher than some value, usually 10 mU/L. Others treat patients with lesser elevations (e.g., 5 to 10 mU/L). Still others consider other factors, such as the presence of symptoms consistent with hypothyroidism, or high serum lipid or antithyroid antibody values, in addition to the magnitude of the elevation in serum TSH, in deciding whether to recommend treatment. A final argument in support of treatment is that it prevents progression to overt hypothyroidism. That is true, but subclinical hypothyroidism is often not persistent, particularly among patients whose serum TSH concentration is 5 to 10 mU/L (see page 41).

In this new review, Villar et al. identified 2513 articles about subclinical hypothyroidism, of which only 12 described randomized clinical trials of T_4 therapy. Their summary analysis revealed little benefit of T_4. However, most of the trials were small; the degree and causes of subclinical hypothyroidism varied; the patients and end points studied, particularly those related to symptoms and quality of life, were heterogeneous; and confounding variables were not uniformly controlled.

The decision to prescribe T_4 for patients with subclinical hypothyroidism must consider cost, benefit, and risk, in particular the risk of overtreatment. This disorder is common, and therefore the implications of widespread treatment are enormous. The continuing lack of evidence of benefit of treatment may be attributed to the weakness of the studies that have been done, but proving benefit will not be easy.

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Serum insulin-like growth factor-1 concentrations are associated with goiter

Volzke H, Friedrich N, Schipf S, Haring R, Lüdemann J, Nauck M, Dörr M, Brabant G, Wallaschofski H. Association between serum insulin-like growth factor-I levels and thyroid disorders in a population-based study. J Clin Endocrinol Metab 2007;92:4039-45.

SUMMARY

Background Insulin-like growth factor 1 (IGF-1) may contribute to thyroid enlargement and the formation of thyroid nodules. To address this possibility, the relationships between serum IGF-1 concentrations and thyroid disorders were determined in a large group of healthy subjects.

Methods The study group consisted of 3662 healthy subjects (1746 women, 1916 men; age range, 27 to 71 years) who were enrolled in a population-based health survey in a region of Germany. Pregnant women and subjects with thyroid disease or taking thyroid hormone or an antithyroid drug were excluded. The demographic and clinical characteristics of the subjects were obtained by interview. Serum IGF-1 and thyrotropin (TSH) were measured by immunoassay, and thyroid volume and the presence of thyroid nodules >1 cm were determined by ultrasonography. Goiter was defined as thyroid volume >18 ml in women and >25 ml in men.

Results The median serum IGF-1 concentrations were 135 ng/ml in the women and 131 ng/ml in the men. When divided into tertiles (<112, 112 to 156, and >156 ng/ml), both the women and men in the respective upper tertile were younger and had lower body-mass-index values than those in the lower tertile. The frequency of smoking was higher in the upper tertile in both women and men. Urinary iodine excretion (range of median values in the three tertiles of women and men, 104 to 136 μg/dl), serum TSH concentrations, and frequency of low serum TSH concentrations were similar in the women and men in each tertile, except that the median serum TSH concentration was slightly higher in the men in the upper tertile.

The frequency of goiter was similar in the women and men in the three tertiles (35, 36, and 31 percent in women and 36, 42, and 37 percent in men). The frequency of thyroid nodules was lower in the women in the upper tertile (30, 22, and 16 percent) but not in the men (18, 18, and 14 percent).

In analyses adjusted for age, higher serum IGF-1 concentrations were associated with goiter in both women and men, thyroid nodules in men, and low serum TSH concentrations in women (Table). The results were similar when the analyses were also adjusted for body-mass index, smoking status, and urinary iodine excretion.

Table. Odds Ratios for Goiter According to Serum IGF-1 Concentrations in Women and Men.

	Serum IGF-1 (ng/ml)		
Goiter	<111	111–156	>156
Women	1.0	1.39*	1.57*
Men	1.0	1.45*	1.92*
Thyroid nodules			
Women	1.0	1.13	1.29
Men	1.0	1.26*	1.52*
Low serum TSH (<0.25 mU/L)			
Women	1.0	1.55*	1.75*
Men	1.0	1.13	1.12

*P for trend, <0.05.

Conclusion Serum IGF-1 concentrations tend to be higher in women and men with goiter, in men with thyroid nodules, and in women with low serum TSH concentrations, suggesting that IGF-1 has weak thyroid-stimulating actions.

COMMENTARY

IGF-1 is a thyroid growth factor, perhaps most evident from the fact that goiter is common in patients with acromegaly (1), but also supported by studies like this. It probably also stimulates thyroid secretion, because serum TSH concentrations tend to be lower in patients with acromegaly, and as found in the women with higher serum IGF-1 concentrations in this study. (Note that the results were not altered by adjustment for smoking, which stimulates thyroid secretion and growth [see page 42].) Conversely, the thyroid gland is small in patients with isolated growth hormone deficiency and low serum IGF-1 concentrations, although their serum TSH concentrations are normal (2). Given that there are two signaling systems—the cyclic AMP–adenylate cyclase system and the phospholipase C system—that mediate thyroid secretion and growth, the relative stimulatory effects of TSH and IGF-1, acting via different receptors, on the two systems may vary.

The thyroid contains growth hormone receptors and IGF-1, as well as IGF-1 receptors. Therefore, it is likely that local production of IGF-1 is a more important determinant of thyroid function and growth than is its systemic production, and that many of the genetic and environmental factors involved in goitrogenesis stimulate local IGF-1 production (3).

Robert D. Utiger, M.D.

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Calcium carbonate and sevelamer decrease thyroxine absorption in hemodialysis patients with hypothyroidism

Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. Effect of phosphate binders upon TSH and L-thyroxine dose in patients on thyroid replacement. Int Urol Nephrol 2007;39:599-602.

SUMMARY

Background Patients with chronic renal insufficiency have hyperphosphatemia, which is treated with a phosphate-binding agent such as calcium acetate, calcium carbonate, or sevelamer (Renagel, which is calcium-free). Calcium carbonate is known to decrease the gastrointestinal absorption of thyroxine (T_4) in normal subjects and patients with hypothyroidism, but whether it or the other two compounds have a similar effect in hemodialysis patients with hypothyroidism is not known. In this study, the effect of these three compounds on serum thyrotropin (TSH) concentrations was determined in hemodialysis patients treated with T_4.

Methods The records of 1566 hemodialysis patients treated at a single facility were searched to identify patients with hypothyroidism who had been taking T_4 and were treated with either calcium acetate, calcium carbonate, or sevelamer. Most of the patients took the T_4 with breakfast. The phosphate binders were taken then and at lunch and dinner. The per-meal doses were, respectively, 667, 650, and 800 mg, which provided equivalent phosphate-binding capacity. Serum TSH was measured every three months for two years after the phosphate binder was started.

Results Sixty-seven hemodialysis patients had hypothyroidism and were taking T_4. Thirty-five (52 percent) were treated with calcium acetate, 19 (28 percent) with calcium carbonate, and 13 (20%) with sevelamer (Table). During the two-year study period, the mean dose of T_4 in the calcium-acetate group was 95 μg daily, and their overall mean serum TSH concentration was 3.9 mU/L. The T_4 dose in the calcium-carbonate group was similar (97 μg daily), and their overall mean serum TSH concentration was higher (23.8 mU/L). The overall T_4 dose in the sevelamer group was higher (137 μg daily), but despite the higher dose their mean overall serum TSH concentration was 20.3 mU/L. Serum phosphate concentrations were similar in the three groups during the study period.

Table. Effects of Calcium Acetate, Calcium Carbonate, and Sevelamer on Overall Serum TSH Concentrations in Hemodialysis Patients Treated with T_4.

	Calcium Acetate (n=35)	Calcium Carbonate (n=19)	Sevelamer (n=13)
Women/men	21/14	15/4	12/1
Age (yr)	72	76	76
T_4 dose (μg/day)	95	99	137
Serum TSH (mU/L)	3.9	23.8	20.3

There was no change in mean quarterly serum TSH concentration during the study in the calcium-acetate group, whereas it increased from 20 to 28 mU/L in the calcium-carbonate group. The increase was even greater, from 5 to 31 mU/L, in the sevelamer group, despite an increase in T_4 dose from 150 to 200 μg daily after six months in four patients in this group. (These values were extrapolated from Figure 1 in the paper, and the first value for the two groups is the value after three months of therapy, not the base-line value.)

Conclusion Calcium carbonate and sevelamer, but not calcium acetate, are associated with an increase in serum TSH concentrations in hemodialysis patients with hypothyroidism who are treated with T_4, presumably caused by decreased gastrointestinal absorption of T_4.

COMMENTARY

Surprisingly little is known about the absorption of T_4, even though it is taken by millions of people, and much of what is known comes from studies in which single high doses of T_4, for example, 400 to 1000 μg, were given. Only doses of this magnitude result in clearly detectable increases in serum T_4 concentrations, which typically are highest 2 to 4 hours after T_4 ingestion in both normal subjects and patients with hypothyroidism. Estimates of fractional T_4 absorption vary from 65 to 85 percent. Most of the absorption occurs in the upper small bowel, and it is facilitated by acid. T_4 absorption may be decreased by food and several medications, including calcium carbonate and ferrous sulfate, and in patients with gastrointestinal disorders.

Calcium carbonate is probably the most widely used medication that decreases T_4 absorption, presumably because of formation of insoluble or at least nonabsorbable calcium-T_4 complexes in the gasatrointestinal tract. The effect of calcium carbonate, as compared with calcium acetate, to decrease T_4 absorption may relate to its greater dissociation in the acid milieu of the stomach, thus facilitating the formation of these complexes (1). This study by Diskin et al. indicates that sevelamer is even more potent in decreasing T_4 absorption than is calcium carbonate. The results would have been clearer had the base-line serum TSH values been similar in all the patients and the T_4 dose increased as needed to maintain normal serum TSH concentrations. In another study, in which normal subjects were given 1000 μg of T_4 alone and in combination with 800 mg of sevelamer on separate occasions while fasting, the peak serum T_4 concentrations and the area under the serum T_4 curve above base line were approximately 50 percent lower after co-administration of T_4 and sevelamer (2).

Impaired absorption of T_4 should always be considered when administration of T_4 has less effect on clinical well-being and serum T_4 and TSH concentrations than expected.

Robert D. Utiger, M.D.

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A *BRAF* gene mutation is common in patients with papillary thyroid carcinoma and is associated with persistent or recurrent tumor

Kebebew E, Weng J, Bauer J, Ranvier G, Clark OH, Duh QY, Shibru D, Bastian B, Griffin A. The prevalence and prognostic value of *BRAF* mutation in thyroid cancer. Ann Surg 2007;246:466-71.

SUMMARY

Background A mutation in the gene for *BRAF*, the B-type of Raf kinase, is the most common genetic change in papillary carcinoma of the thyroid. This is a missense mutation in which adenine is substituted for thymine (T1799A), resulting in substitution of glutamic acid for valine (V600E) in the Raf kinase. The mutation leads to constitutive activation of the kinase, which in turns leads to activation of the mitogen-activating protein kinase pathway and thyroid-cell growth and proliferation. This study was done to determine the relationships between this *BRAF* mutation and the histologic characteristics of thyroid carcinomas and the clinical characteristics and prognosis of patients with tumors with the mutation.

Methods The study subjects were 347 patients (264 women, 83 men; mean age, 46 years) with thyroid carcinoma. The tumor was a papillary carcinoma, classic variant, in 245 patients (71 percent); a papillary carcinoma, follicular variant, in 29 (8 percent); and a follicular carcinoma in 73 (21 percent). The mean tumor size was 2.7 cm. The tumor was multicentric in 109 patients (31 percent), 82 (24 percent) had extrathyroidal extension, and 115 (33 percent) had lymph-node metastases. Treatment consisted of total or near-total thyroidectomy in 281 patients (81 percent) and a lesser thyroid resection in the remainder, and 267 (77 percent) were treated with iodine-131 (I-131). The mean duration of follow-up was 72 months.

Genomic DNA was extracted from fresh-frozen and paraffin-embedded tissue and the *BRAF* gene was amplified by the polymerase chain reaction followed by sequencing of the reaction products.

Results The mutation coding for the *BRAF* V600E product was found most often in the classic papillary carcinomas and least often in the follicular carcinomas (Table).

The tumor and one lymph-node metastasis was analyzed in 32 patients: 13 had the mutation in both tissues, 14 had no mutation in either tissue, and the results were discordant in 5 (3 had the mutation only in the tumor and 2 only in the nodal metastasis). Among 2 patients in whom the tumor and 2 nodes were analyzed, 2 had the mutation in all sites and 1 had no mutation in any site.

Table. Frequency of *BRAF* V600F Mutation in 347 Thyroid Carcinomas.

	No.	*BRAF* Mutation – No.
Papillary carcinoma, classic variant	245	126 (51%)
Papillary carcinoma, follicular variant	29	7 (24%)
Follicular carcinoma	73	1 (1%)

In the patients with both variants of papillary carcinoma, the presence of the *BRAF* mutation was correlated with older age, high AMES (Age, Metastases, Extrathyroidal invasion, and Size) risk group, and recurrent or persistent carcinoma, but not tumor size, lymph-node metastases, or multicentric tumors.

In the patients with classic papillary carcinoma, the presence of the mutation was associated with older age, higher tumor stage, lymph-node metastases, and recurrent or persistent carcinoma. In these same patients, the risk factors for recurrent or persistent tumor were larger tumor size, extrathyroidal invasion, lymph-node metastases, tumor stage, *BRAF* V600E mutation, extent of thyroidectomy, and I-131 therapy. Among patients with small (≤2 cm) carcinomas, the rate of recurrent or persistent carcinoma was higher in those with the *BRAF* mutation, as compared with those without this mutation (approximately 38 vs. 17 percent, extrapolated from Figure 1 in the paper), and the rate also was higher among the patients with low AMES risk tumors with *BRAF* mutations (37 vs. 19 percent).

Conclusion The *BRAF* V600F mutation is a prominent feature of the classic variant of papillary carcinoma, and is also present in some follicular-variant papillary carcinomas, but is rarely present in follicular carcinomas. In patients with the classic variant of papillary carcinoma, the presence of the mutation is associated with more extensive disease and a higher risk of recurrent or persistent carcinoma.

COMMENTARY

These results confirm those of other, smaller studies, as compiled from the literature (1), in which about 60 percent of classic papillary carcinomas carried the *BRAF* V600E mutation, as compared with 12 percent of the follicular variant of papillary carcinomas and 0 percent of follicular carcinomas. There are differences in the frequency of the mutation in different patient groups; for example, the mutation is less common in papillary carcinomas in younger patients and those with radiation-related papillary carcinoma (most of whom are young). The evidence that the prognosis of patients with papillary carcinomas that carry this mutation have a poorer prognosis is good, and the higher frequency of the mutation (77 percent [1]) in the tall-cell type of papillary carcinoma is consistent with the poorer prognosis of patients with this tumor (see page 52).

Is genotyping papillary carcinomas for this *BRAF* mutation useful in guiding therapy? Probably not now, but maybe soon. For example, patients with *BRAF*-negative papillary carcinoma may not need I-131 therapy, or they may need less aggressive follow-up. Also, the presence or absence of the mutation may eventually direct chemotherapy.

Robert D. Utiger, M.D.

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Patients with the tall-cell variant of papillary carcinoma have recurrences more often than do patients with the classic variant

Ghossein RA, Leboeuf R, Patel KN, Rivera M, Katabi N, Carlson DL, Tallini G, Shaha A, Singh B, Tuttle RM. Tall cell variant of papillary thyroid carcinoma without extrathyroid extension: biologic behavior and clinical implications. Thyroid 2007;17:655-61.

SUMMARY

Background There are several types of papillary carcinomas of the thyroid, the most common of which are the classical and follicular variants. The tall-cell variant is less common, but extrathyroidal extension is more common, and this tumor is considered to be more aggressive than the classical variant. In this study the characteristics and course of patients who had the tall-cell or classic variants with no extrathyroidal extension were compared.

Methods Review of the surgical pathology records of the Memorial Sloan-Kettering Cancer Center from 1993 to 2004 revealed 62 cases of the tall-cell variant of papillary carcinoma and 83 cases of the classic variant of papillary carcinoma, none of which had extension of the tumor into the perithyroidal adipose tissue. Patients with lymph-node metastases were not excluded. The pathologic diagnoses were confirmed by three pathologists independently.

The definition of the tall-cell variant was a tumor in which ≥50 percent of the cells were two or more times taller than they were wide (in most tumors the height of the cells was three times their width), the ratio of the nuclear area to the cytoplasmic area was low, and the nuclei had the characteristic appearance of papillary carcinoma (large irregular clear nuclei with grooves and pseudoinclusions) (Figure). The definition of the classic variant was a tumor in which <30 percent of the cells were tall and the nuclei had the same characteristics.

The clinical, pathologic, and follow-up data for the two groups were compared.

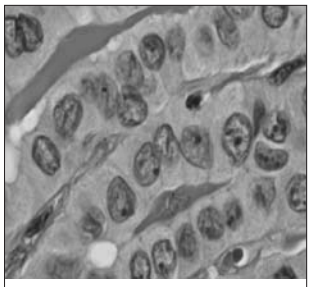

Figure. Photomicrograph of a tall-cell carcinoma (see text for definition of tall cells). H and E, ×400. Courtesy of Vania Nose, M.D., Ph.D.

Results The characteristics of the patients and the tumors in the two groups at the time of diagnosis were similar, except that capsular invasion, lymph-node metastases, and extension into the thyroid capsule were more common in the tall-cell group (Table). Most patients in both groups were treated by total thyroidectomy and lymph-node dissection, and approximately 60 percent in each group were treated with I-131.

Table. Clinical and Tumor Characteristics in Patients with Tall-Cell or Classic Subtypes of Papillary Carcinoma.

	Tall-Cell Variant (n=62)	Classic Variant (n=83)
Women/men	51/11	65/18
Median age (yr)	41	39
Median tumor size (cm)	1.5	1.6
Capsular invasion	70%*	43%
Vascular invasion	5%	0%
Lymph-node metastases	67%*	40%
Extension into thyroid capsule	52%*	23%
Multifocal tumor	39%	24%

*P≤0.05, as compared with the classic subtype.

Complete follow-up data were available for 109 patients in the two groups. During a median follow-up period of 2.9 years, 7 of 47 patients (15 percent) in the tall-cell group and 4 of 62 patients (6 percent) in the classic group had recurrences. Many were lymph-node recurrences in patients with node metastases initially, but 3 patients in the tall-cell group had lung metastases.

Conclusion Patients with the tall-cell variant of papillary carcinoma who do not have extrathyroidal extension of the carcinoma at the time of diagnosis are more likely to have recurrences than are similar patients with the classic variant of papillary carcinoma.

COMMENTARY

The tall-cell variant of papillary carcinoma is often considered to be one of the group of poorly differentiated thyroid carcinomas, which also include columnar-cell carcinoma, diffuse sclerosing papillary carcinoma, solid carcinoma, and insular carcinoma (1). They are considered more aggressive than classic papillary carcinoma or the follicular variant of papillary carcinoma, but less aggressive than anaplastic carcinoma. However, these tumors are uncommon, there are variations in the pathologic criteria used to diagnose them (e.g., what proportion of cells must be tall to warrant the diagnosis of tall-cell carcinoma?), and there is probably reporting bias, in that patients with more extensive disease are more likely to be reported. One reason not to consider the tumors together is that the nuclear features of papillary carcinoma are prominent only in tall-cell, diffuse sclerosing, and solid carcinomas.

This study concerned only patients who had no extrathyroidal extension of their tumor, irrespective of whether it was a tall-call variant or a classic variant, in an attempt to compare tumors of similar size and extent. The two most important prognostic characteristics of patients with thyroid carcinoma—age and tumor size—were similar, but the tall-cell carcinomas had more of the histologic features associated with a poorer prognosis, such as capsular invasion and extension into the thyroid capsule, and the patients in the tall-cell group were more likely to have lymph-node metastases at base line and to have lymph-node and pulmonary recurrences. These results provide further evidence that the tall-cell variant of papillary carcinoma is more aggressive than the classic variant.

Robert D. Utiger, M.D.

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Thyroidectomy in patients with papillary and follicular carcinoma is rarely complete

Salvatori M, Raffaelli M, Castaldi P, Treglia G, Rufini V, Perotti G, Lombardi CP, Rubello D, Ardito G, Bellantone R. Evaluation of the surgical completeness after total thyroidectomy for differentiated thyroid carcinoma. Eur J Surg Oncol 2007;33:648-54.

SUMMARY

Background Many patients with thyroid carcinoma who are treated by total thyroidectomy are found postoperatively to have tissue in the thyroid bed, indicating that the thyroidectomy was not complete. This study was done to evaluate systematically the completeness of total thyroidectomy in patients with thyroid carcinoma.

Methods The study subjects were 720 patients (572 women, 148 men; mean age, 49 years) with thyroid carcinoma treated by total thyroidectomy at a single hospital between 1998 and 2004. The tumor was a papillary carcinoma in 628 patients (87 percent) and a follicular carcinoma in 92 (13 percent); the tumor–node–metastasis (TNM) stage was 1 in 198 patients (27 percent), 2 in 381 (53 percent), 3 in 128 (18 percent), and 4 in 13 (2 percent). Patients who had lymph-node or distant metastases or high serum antithyroglobulin antibody concentrations were excluded.

Two to 4 months after surgery, after cessation of thyroxine (T_4) therapy, serum thyroglobulin (Tg) and 24-hour thyroid iodine-131 (I-131) uptake were measured. The patients then were treated with 50 to 150 mCi (1850 to 5550 MBq) (mean, 54 mCi [2000 MBq] of I-131, followed 2 to 5 days later by whole-body scans. The number of thyroid remnants was determined from post-I-131-therapy scans of the region from the thyroid cartilage to the suprasternal notch.

All patients in whom the post-I-131-therapy scan revealed thyroid remnants were reevaluated, including a diagnostic whole-body I-131 scan, 6 to 10 months later after cessation of T_4 therapy. Successful I-131 therapy was defined as a 24-hour I-131 uptake ≤1 percent, no visible thyroid uptake on the follow-up diagnostic I-131 scan, and a serum Tg concentration ≤2 ng/ml. Patients who had I-131 uptake in the thyroid bed at this time were treated with I-131 again.

Results The post-I-131-therapy scan revealed no thyroid tissue in 50 of the 720 patients (7 percent). Their mean 24-hour thyroid I-131 uptake was 0.3 percent (range, 0.1 to 1.0), and all had serum Tg concentrations ≤2 ng/ml. The best predictors of the absence of visible I-131 uptake on the post-therapy scan were a 24-hour thyroid I-131 uptake ≤1 percent and a serum Tg value ≤2 ng/ml.

The post-I-131-therapy scans revealed foci of uptake in the thyroid region in 670 patients (93 percent). Their mean 24-hour thyroid I-131 uptake was 2.9 percent (range, 1.1 to 9.8) and their serum Tg concentration was 8.0 ng/ml (range, 2.3 to 69). The foci of I-131 uptake were located as follows: right thyroid lobe, 34 percent; left thyroid lobe, 28 percent; the extreme upper-pole region of both lobes, 18 percent; and the pyramidal lobe and thyroglossal duct region, 20 percent. Foci of uptake were present slightly less often in the lobe that contained the carcinoma than the contralateral lobe.

The I-131 therapy successfully destroyed the thyroid remnant(s) in 610 of these 670 patients (91 percent), including 582 of the 656 patients (89 percent) who received 50 mCi (1850 MBq) and 28 of the 41 patients (68 percent) who received 100 mCi (3700 MBq).

Conclusion Most patients with papillary or follicular carcinoma of the thyroid who undergo total thyroidectomy have residual thyroid tissue, as determined by not only post-I-131 therapy imaging, but also a 24-hour thyroid I-131 uptake >1 percent and a serum Tg concentration >2 ng/ml when they are hypothyroid.

COMMENTARY

This retrospective study of patients with thyroid carcinoma suggests that total thyroidectomy is a myth, even when done at a center that specializes in treatment of patients with thyroid carcinoma. The low rate of complete thyroidectomy of 7 percent raises important questions regarding this operation. Why isn't the operation complete more often? Do metastases in lymph nodes in the central compartment of the neck account for some of the residual thyroid tissue?

In this study, 38 percent of the remnants were in the extreme upper pole regions or the pyramidal-lobe and thyroglossal-duct regions. This surprising finding indicates that thyroid tissue often extends more superiorly than expected. Finding remnant thyroid tissue in the mid region of a thyroid lobe is less surprising, because that is adjacent to where the recurrent laryngeal nerve enters the larynx, and the importance of preserving this nerve may lead to the preservation of some thyroid tissue. Not surprising is the finding of remnants in the lobe opposite to the tumor more often than in the lobe containing the tumor, indicative of more complete resection of the lobe containing the tumor. Another explanation for the low rate of complete thyroidectomy is that some patients had occult metastases in lymph nodes in the thyroid bed or adjacent to it. Given the high rate of remnant destruction, these metastases as well as the remnants of normal thyroid tissue were destroyed by the I-131 therapy.

Determining the completeness of thyroidectomy is important for several reasons. If thyroidectomy is truly complete, there is no need for postoperative I-131 therapy. If it is incomplete, some information about the size and the avidity of the remnant(s) for I-131 will help to determine the dose of I-131 needed to destroy it. It is therefore important for thyroid surgeons to communicate accurately the true extent of thyroidectomy.

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The outcome of papillary thyroid carcinoma in patients with hyperthyroidism caused by Graves' disease is similar to that in euthyroid patients

Yano Y, Shibuya H, Kitagawa W, Nagahama M, Sugino K, Ito K, Ito K. Recent outcome of Graves' disease patients with papillary thyroid cancer. Eur J Endocrinol 2007;157:325-9.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease also have thyroid carcinoma, which may be more aggressive than in euthyroid patients, perhaps because of the thyroid-stimulating actions of thyrotropin (TSH) receptor-stimulating antibodies (TSHR-Ab). In this case–control study, the outcome of papillary thyroid carcinoma in patients with Graves' hyperthyroidism and euthyroid patients was compared.

Methods Between 1994 and 2004, thyroid ultrasonography was done in 32,200 patients with Graves' hyperthyroidism, defined as hyperthyroidism, diffuse goiter, and a high serum concentration of TSHR-Ab (measured by receptor assay), at a single clinic in Japan. Fine-needle aspiration was done in patients who had thyroid nodules; the cytology was diagnostic or suspicious for carcinoma in 178 patients (0.6 percent). The nodule proved to be a papillary carcinoma in 157 patients, a follicular carcinoma in 8 patients, and a medullary carcinoma in 1; the latter 9 patients and another 48 patients who had an incidental papillary carcinoma in the resected thyroid tissue were not studied further. Among the 157 patients with papillary carcinoma, 134 were treated by total or subtotal thyroidectomy and lymph-node dissection, 20 by lobectomy and node dissection, and 3 by lobectomy.

This study was done in 154 patients with Graves' hyperthyroidism who had papillary carcinoma (3 were lost to follow-up) and 176 euthyroid patients with papillary carcinoma matched for age, sex, and tumor size who were operated on at the same time. The extent of surgery in this group is not described. All the patients were followed with measurements of serum thyroglobulin, ultrasonography, and other imaging studies as indicated. The median follow-up period was 50 months in the hyperthyroid group and 54 months in the euthyroid group.

Results The characteristics of the patients and the papillary carcinomas in the two groups were similar (Table).

Table. Characteristics of the Patients in the Hyperthyroid and Euthyroid Groups and of Their Tumors.

	Hyperthyroid Group (n=154)	Euthyroid Group (n=176)
Women/men	135/19	151/25
Median age – yr (range)	50 (16-76)	51 (17-75)
Median tumor diameter – cm (range)	0.9 (0.1-7.0)	1.0 (0.2-7.5)
Patients with multifocal tumors	54 (35%)	50 (28%)
Patients with lymph-node metastases	69 (45%)	97 (55%)
Patients with distant (lung) metastases	2 (1%)	3 (2%)

There was a weak inverse correlation between serum TSHR-Ab concentrations and tumor size (r=–0.19; P=0.02). The concentrations were not correlated with the presence of multifocal carcinoma or lymph-node metastases.

During follow-up, 6 patients in the hyperthyroid group (4 percent) and 18 in the euthyroid group (10 percent) had persistent or new lymph-node metastases, and 1 (1 percent) and 4 patients (2 percent), respectively, had distant metastases. One patient in the hyperthyroid group and 2 patients in the euthyroid group died of metastatic thyroid carcinoma.

Seven patients in the hyperthyroid group had recurrent hyperthyroidism after surgery, none of whom had recurrent thyroid carcinoma.

Conclusion The characteristics, course, and outcome of papillary carcinoma identified by ultrasonography in patients with Graves' hyperthyroidism are similar to those in matched euthyroid patients with carcinomas of similar size.

COMMENTARY

There is some evidence that papillary carcinomas are more common and more aggressive in patients with Graves' hyperthyroidism than in other patients (1), a possible mechanism being initiation and stimulation of tumor growth by TSHR-Ab. The results of this study do not address the frequency issue, but they provide no support for the hypothesis that papillary carcinomas are more aggressive in patients with Graves' hyperthyroidism.

The frequency of multifocal carcinomas and of lymph-node and distant metastases at base line and during follow-up were similar in the hyperthyroid and euthyroid groups. Within the hyperthyroid group, there was no correlation between serum TSHR-Ab values and the presence of multiple tumors or lymph-node metastases at base line. Even the inverse correlation between serum TSHR-Ab values and tumor size argues against a role for the antibodies, but the correlation was weak and should probably be considered a chance finding.

Patients with Graves' hyperthyroidism who have a diffuse goiter and a palpable thyroid nodule should be evaluated in the same way as any other patient with a palpable nodule. (If there is hyperthyroidism, no goiter, and only a nodule, then radioiodine imaging is indicated because the patient may have a thyroid adenoma.) Should ultrasonography or radioiodine imaging be done if no nodule is palpable? No, not in the absence of evidence that thyroid nodules in patients with Graves' hyperthyroidism are more likely to be carcinomas than they are in euthyroid patients, and in the presence of evidence that carcinomas in Graves'-disease patients are not more aggressive than in euthyroid patients.

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Patients with metastatic papillary or follicular carcinoma at diagnosis should be treated aggressively

Sampson E, Brierley JD, Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer 2007;220:1451-6.

SUMMARY

Background A thyroid nodule is the presenting manifestation in most patients who have a carcinoma of the thyroid. However, a few patients have distant metastases at the time of diagnosis. This study was done to determine the outcome of patients with thyroid carcinoma who had metastatic disease at the time of diagnosis and the impact of therapy on outcome.

Methods The study subjects were 49 patients with papillary or follicular carcinoma of the thyroid who had pulmonary, bone, or other distant metastases at the time of diagnosis seen at a single center in Canada between 1980 and 2000. They constituted 6 percent of all patients with these types of carcinoma seen during this time interval. The metastases were detected by clinical examination and imaging procedures, including x-rays, computed tomography, ultrasonography, and iodine-131 (I-131) scans. The avidity of tumor masses for I-131 was evaluated by inspection of scans done after the first dose of I-131 when the patients were hypothyroid.

The patients' records were reviewed to obtain information about the details of the disease (stage, location, size, histology), treatment, follow-up, and outcome.

Results The 49 patients included 34 women and 15 men. Their median age was 68 years (range, 17 to 90); 8 were ≤45, 9 were 45 to 60, and 32 were >60. Twenty-five patients (51 percent) had papillary carcinoma (classical or follicular subtypes) and 24 (49 percent) follicular carcinoma, including 4 with Hürthle-cell carcinoma. The location of the metastases and tumor stages are shown in the Table.

Forty patients (82 percent) were treated with total thyroidectomy (the other 9 declined surgery or the tumor was not resectable), 43 (88 percent) with I-131 (median dose, 150 mCi [5550 MBq]), 39 (80 percent) with external-beam radiation to the neck or metastases, and 14 (28 percent) by excision of a metastasis (mostly bone). The metastases were I-131-avid in 29 patients (67 percent), and 30 patients (70 percent) received multiple doses of I-131.

Twenty-four patients (49 percent) died during a median follow-up period of 3.5 years (range, 0.2 to 16.2), of whom 17 (71 percent) died of thyroid carcinoma. Among the 25 patients (51 percent) who survived, only 4 (16 percent) had no evidence of disease at last follow-up (all had diffuse lung metastases at diagnosis). Favorable prognostic factors were young age, lung (vs. bone) metastases, papillary (vs. follicular) carcinoma, and I-131 avidity.

Conclusion The prognosis of patients with papillary or follicular carcinoma who have metastases at the time of initial diagnosis is poor, but may be improved by aggressive I-131 therapy.

Table. Sites of Distant Metastases and Thyroid and Nodal Stages at the Time of Initial Diagnosis in 49 Patients with Thyroid Carcinoma.

Site of metastasis	No. (%)
Lung only (all diffuse lesions)	22 (45)
Bone only	19 (39)
Other single sites (brain, liver)	2 (4)
Multiple (usually lung and bone)	6 (12)
Stage*	
T1	2 (4)
T2–4	37 (76)
Tx	10 (20)
N0	11 (22)
N1	15 (31)
Nx	23 (47)

*American Joint Committee on Cancer TMN (tumor, node, metastasis) classification.

COMMENTARY

Patients like these are fortunately rare, but they are a reminder that the prognosis of patients with papillary or follicular carcinoma is not always very good. They also serve as a reminder that I-131 therapy can be beneficial in patients with obvious metastatic disease, and that it should be given repeatedly in patients with I-131-avid metastases. For patients in whom I-131 is no longer effective, several new drugs are being evaluated (1).

A broader question is what should be done to identify patients like these from among the many more patients whose tumor is confined to the thyroid, or at least the neck, at the time of initial evaluation. Unfortunately, Sampson et al. do not describe what clinical findings led to the detection of the metastases in their patients.

It is certainly appropriate to ask about symptoms such as dyspnea or bone pain that might indicate the presence of lung or bone metastases, and if symptoms are present to order the appropriate radiologic studies. However, it seems inappropriate to order radiologic studies in patients whose only finding is a palpable or incidentally detected thyroid nodule that is suspected to be a thyroid carcinoma.

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Reference

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Women with hyperthyroidism caused by Graves' disease may have postpartum thyroiditis or postpartum exacerbation of Graves' disease

Tagami T, Hagiwara H, Kimura T, Usui T, Shimatsu A, Naruse M. The incidence of gestational hyperthyroidism and postpartum thyroiditis in treated patients with Graves' disease. Thyroid 2007;17:767-72.

SUMMARY

Background Women with hyperthyroidism due to Graves' disease may have transient or persistent hyperthyroidism during pregnancy and postpartum thyroiditis or a postpartum exacerbation of Graves' hyperthyroidism. This study was done to determine the frequency and characteristics of these types of hyperthyroidism in women with Graves' disease.

Methods The study subjects were 34 women with Graves' hyperthyroidism (mean age, 31 years) who were followed during and for one year after 39 pregnancies. (Most results are given as numbers of pregnancies, rather than numbers of women, and that will be done here.) The women were in remission before 16 pregnancies, and were treated with an antithyroid drug during 23 pregnancies. Among the latter, the drug was stopped during 11 pregnancies and was continued throughout the pregnancy in 12. Serum TSH, free thyroxine (T_4), free triiodothyronine (T_3), human chorionic gonadotropin (HCG), and TSH-receptor antibodies (TSHR-Ab, receptor assay) were measured at one- to three-month intervals during pregnancy, one month after delivery, and at one- to three-month intervals for one year after delivery.

Transient gestational hyperthyroidism was defined as hyperthyroidism and high serum HCG concentrations during the first trimester that subsided spontaneously, and persistent gestational hyperthyroidism as an exacerbation of hyperthyroidism during pregnancy that was treated with an antithyroid drug. Postpartum thyroiditis was defined as transient postpartum hyperthyroidism followed by transient hypothyroidism, or either alone, lasting no more than three months, and postpartum exacerbation of Graves' disease as hyperthyroidism lasting for at least four months.

Results Transient gestational hyperthyroidism occurred during 10 of the 39 pregnancies (26 percent) in the 34 women. It was more frequent in the postpartum-exacerbation group (5 of 11 pregnancies [46 percent]) than in the postpartum-thyroiditis group (4 of 17 [24 percent]) or the no-postpartum-hyperthyroidism group (1 of 11 [9 percent]). Persistent gestational hyperthyroidism occurred during 3 pregnancies, 1 in the postpartum-thyroiditis group and 2 in the postpartum-exacerbation group. Peak serum HCG concentrations were higher during the pregnancies with transient gestational hyperthyroidism than in the other pregnancies (240,000 vs.133,000 IU/ml).

Seventeen pregnancies (44 percent) were followed by postpartum thyroiditis. It was characterized by transient hyperthyroidism followed by hypothyroidism after 11 pregnancies (65 percent), transient hyperthyroidism alone after 5 (29 percent), and transient hypothyroidism after 1 (6 percent). Eleven pregnancies (28 percent) were followed by postpartum exacerbation of Graves' hyperthyroidism (Table). The mean time to onset of hyperthyroidism was 4.5 months in the postpartum-thyroiditis group, as compared with 5.2 months in the postpartum-exacerbation group. The peak serum free T_4 and free T_3 concentrations, ratio of serum free T_3 to free T_4, and serum TSHR-Ab concentrations were higher in the postpartum-exacerbation group.

Table. Features of Thyroid Dysfunction in Pregnancies Followed by Postpartum Thyroiditis or Postpartum Exacerbation of Graves' Hyperthyroidism in Women with Graves' Hyperthyroidism before Pregnancy.

	Postpartum Thyroiditis (n=17)	Postpartum Exacerbation (n=11)
Time of onset (mo)	4.5	5.2
Serum free T_4 (ng/dl)	2.8	3.9
Serum T_3 (ng/dl)	0.7	1.2
Serum free T_3/free T_4 ratio (ng/ng)	0.2	0.3
Serum TSHR-Ab (IU/L)	1.4	72.5

Reference values: free T_4, 1.0 to 1.8 ng/dl; and free T_3, 0.2 to 0.4 ng/dl. To convert serum free T_4 and free T_3 values to pmol/L, multiply by 12.9 and 15.4, respectively.

Conclusion Women with Graves' hyperthyroidism in the past or during pregnancy may have either postpartum thyroiditis or postpartum exacerbation of Graves' disease.

COMMENTARY

Transient gestational hyperthyroidism is due to the weak thyroid-stimulating activity of HCG (or rarely to the presence of a mutation in the TSH receptor that increases the thyroidal action of HCG). It is transient because serum HCG concentrations are high for a relatively short time during early pregnancy. Although not mentioned in this report, most women with transient gestational hyperthyroidism have hyperemesis gravidarum, probably caused by excessive estrogen production. It is not surprising that women with Graves' disease are susceptible to transient gestational hyperthyroidism, because of the additive thyroid-stimulating actions of HCG and TSHR-Ab, whereas in normal women the thyroid-stimulating action of HCG would to some extent be counterbalanced by a fall in TSH secretion.

Graves' disease tends to diminish, even disappear, during pregnancy, but may recur after pregnancy. This fluctuating course of the disease, and therefore the disappearance and then recurrence of hyperthyroidism, is attributed to changes in maternal immune tolerance, abetted by changes in the production of thyroxine-binding globulin that increase and then decrease, respectively, serum binding of T_4 and T_3.

What is less clear is why postpartum thyroiditis should be so frequent in women with Graves' disease (17 of 39 pregnancies). They were women in whom Graves' disease remained in remission, as indicated by their much lower serum TRAb concentrations when hyperthyroid after pregnancy (Table). Evidently, their thyroid autoimmune disease had evolved from one characterized by thyroid stimulation (Graves' disease) to one characterized by transient thyroid inflammation (autoimmune thyroiditis).

Robert D. Utiger, M.D.

Patients with silent thyroiditis may have multiple recurrences

Mittra ES, McDougall IR. Recurrent silent thyroiditis: a report of four patients and review of the literature. Thyroid 2007;17:671-5.

SUMMARY

Background Silent (painless) thyroiditis is characterized by transient hyperthyroidism followed by transient hypothyroidism and then recovery. Repeated episodes are rare. This report describes four patients who had repeated episodes of painless thyroiditis, three of whom were ultimately treated with radioiodine to prevent recurrence.

Case 1 This man was 38 years old at the time of his first episode of silent thyroiditis in 1979. He subsequently had eight more episodes at approximately 3-year intervals. Four months after the last episode, when he was hypothyroid, his 24-hour thyroid radioiodine uptake was 19 percent. He was treated with radioiodine and then thyroxine (T_4), and since then he has not had a recurrence.

Case 2 This woman had one probable and three definite episodes of silent thyroiditis in 8 years. She was treated with T_4 when hypothyroid after her second episode. She later had two more episodes of silent thyroiditis while taking T_4. She was treated with radioiodine when her 24-hour thyroid radioiodine uptake was 46 percent during recovery after the last episode in 1992. She became hypothyroid three months later, was treated with T_4, and has not had a recurrence since then.

Case 3 This woman was 27 years old when she had her first episode of silent thyroiditis in 1997. She had additional episodes in 2000 and 2002. She was treated with radioiodine while hypothyroid during the third episode in 2002 (24-hour thyroid radioiodine uptake, 66 percent). She became hypothyroid two months later, was treated with T_4, and has not had another recurrence.

Case 4 This man was 24 years old when he had silent thyroiditis in 2002, with hyperthyroidism for two months, followed by transient subclinical hypothyroidism. His second episode of silent thyroiditis was in 2006.

Summary of Cases These four patients had from two to nine episodes of silent thyroiditis, including two episodes during T_4 therapy in one patient. The intervals between the episodes ranged from 1 to 4 years (mean, 2.9).

The episodes were characterized by transient symptomatic hyperthyroidism, for the most part documented by high serum free T_4 and low serum thyrotropin concentrations, and low 24-hour thyroid radioiodine uptake values at the same time, providing documentation of the diagnosis of thyroiditis. The duration of hyperthyroidism was 4 to 8 weeks. None of the patients had neck pain or tenderness at any time.

The episodes of transient hyperthyroidism were followed by transient hypothyroidism, usually subclinical hypothyroidism, during which two patients (cases 2 and 3) had high thyroid radioiodine uptake values, followed by recovery and normal thyroid function until the next episode of painless thyroiditis.

Three patients were ultimately treated with radioiodine to induce hypothyroidism, with the goal of preventing future episodes, so far with success.

Conclusion Silent thyroiditis is a cause of transient hyperthyroidism that may be followed by transient hypothyroidism. It occurs sporadically and may be recurrent. Recurrences may be prevented by induction of hypothyroidism with radioiodine, but not administration of T_4.

COMMENTARY

The term silent thyroiditis is something of a misnomer, because it is silent only in the sense that it is not associated with thyroid pain and tenderness. It can cause symptomatic hyperthyroidism, and less often symptomatic hypothyroidism. Recurrences are rare, but in three patients in this study repeated recurrences led to thyroid ablation, on the reasonable assumption that if there was no thyroid there could be no recurrence. The perhaps equally reasonable and less drastic assumption, that inducing thyroid atrophy by giving T_4 might also reduce the likeli-hood of recurrence, seems not to be valid, at least it was not effective in one patient in this study. Glucocorticoid therapy, which shortens the duration of silent thyroiditis (1), might also reduce recur-rence, but seems a rather drastic solution.

Little is known about the frequency and natural history of sporadic silent thyroiditis, as compared with silent thyroiditis in postpartum women, usually defined as occurring ≤1 year after delivery or miscarriage, nor has a preceding event like pregnancy been identified. (Silent thyroiditis has been described in patients treated with lithium, amiodarone, and interferon-α and other cytokines.) The clinical manifestations, course, and pathology (lymphocytic thyroiditis with few or no germinal centers) of silent thyroiditis and postpartum thyroiditis are similar. Prospective clinical and biochemical studies in postpartum women have revealed that postpartum thyroiditis occurs after 5 to 10 percent of pregnancies (2), many of the women are asymptomatic, and recurrences after subsequent pregnancies are common (3). This type of information about sporadic silent thyroiditis is not available, but it is probably a common cause of subclinical or even overt hyperthyroidism found in surveys in which serum TSH was measured in healthy people.

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The clinical and pathologic features of thyroid autoimmunity are usually concordant in patients with thyroid nodules and do not predict the presence of thyroid carcinoma

Rago T, Di Coscio G, Ugolini C, Scutari M, Basolo F, Latrofa F, Romani R, Berti P, Grasso L, Braverman LE, Pinchera A, Vitti P. Clinical features of thyroid autoimmunity are associated with thyroiditis on histology and are not predictive of malignancy in 570 patients with indeterminate nodules on cytology who had a thyroidectomy. Clin Endocrinol (Oxf) 2007;67:363-9.

SUMMARY

Background Chronic autoimmune thyroiditis may be defined on the basis of serologic, ultrasonographic, and histopathological findings. In this study, the relationships between these findings were evaluated in patients with thyroid nodules who underwent thyroidectomy, and the findings were correlated with the presence of thyroid carcinoma.

Methods The study subjects were 570 patients (446 women, 124 men; mean age, 45 years) who had a hypofunctioning thyroid nodule, with a cytologic diagnosis of follicular or oncocytic (Hürthle-cell) tumor. All patients had measurements of serum antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) antibodies, determination of thyroid echogenicity by ultrasonography, and assessment of lymphocytic infiltration of the nodule and the extranodular tissue. Hypoechogenicity was categorized as mild, moderate, and marked, as compared with normal thyroid tissue. All patients then underwent partial or total thyroidectomy. The nodules were determined to be benign or malignant, and lymphocytic infiltration of both the nodules and extranodular regions was graded as absent (<10 lymphocytic cells/low-power field, mild (<50 cells/field), moderate (50 to 100 cells/field), and severe (>100 cells/field).

Results

Thyroid Autoimmunity Serum anti-TPO antibody or anti-Tg antibody concentrations were high in 122 of the 570 patients (21 percent), and both were high in 57 patients (10 percent). Diffuse thyroid echogenicity was present in 115 patients (20 percent); it was graded as mild in 98 (17 percent) and moderate to marked in 17 (3 percent). Lymphocytic infiltration was present in 117 patients (20 percent); and was moderate in 76 patients (13 percent) and severe in 41 (7 percent).

There was concordance between the three features of thyroid autoimmune disease (Table). For example, 36 percent of the patients with high serum antithyroid antibody concentrations had thyroid hypoechogenicity, as compared with 16 percent of the patients with normal concentrations.

Table. Relationships between Serum Antithyroid Antibody (Anti-TPO or Anti-Tg) Concentrations, Thyroid Echogenicity, and Lymphocytic Infiltration in 570 Patients with Thyroid Nodules.

Serum antithyroid antibodies	Echogenicity		Lymphocytic Infiltration	
	Decreased	Normal	Present	Absent
High (n=122)	44 (36%)	78 (64%)	64 (52%)	58 (48%)
Normal (n=448)	71 (16%)	377 (84%)	53 (12%)	395 (88%)
Lymphocytic infiltration				
Present (n=117)	42 (36%)	75 (64%)		
Absent (n=453)	73 (16%)	380 (84%)		

Nodule Pathology The thyroid nodule was a carcinoma in 135 of the 570 patients (24 percent); 110 (81 percent) were papillary carcinomas (mostly the follicular-variant subtype), 16 (12 percent) minimally invasive follicular carcinomas, and 9 (7 percent) other types. Among the 435 patients with benign nodules (76 percent), most 392 (90 percent) were follicular or oncocytic adenomas or hyperplastic nodules.

None of the three features of thyroid autoimmune disease was associated with nodule pathology. For example, there was lymphocytic infiltration of the thyroid in 28 of the 135 patients (21 percent) with thyroid carcinoma and 89 of the 435 (20 percent) with a benign nodule. Among the 117 patients with lymphocytic infiltration, there was infiltration of the nodule as well as the extranodular tissue in 106 (91 percent).

Conclusion Among patients with thyroid nodules, the serologic, ultrasonographic, and histopathologic features of thyroid autoimmune disease are often concordant, and the frequency of these findings is similar in patients with thyroid carcinoma and those with benign nodules.

COMMENTARY

This study addressed several questions. One is the relative value of high serum antithyroid antibody concentrations, thyroid hypoechogenicity, or lymphocytic infiltration of the thyroid as an indicator of autoimmune thyroid disease. There was substantial concordance, and it is not likely to have been altered by the fact that the patients' presenting problem was a thyroid nodule, rather than a diffuse goiter, subclinical hypothyroidism, or any one of the three findings.

A second question is the frequency of carcinoma in nodules with a cytologic diagnosis of follicular or oncocytic (Hürthle-cell) tumor. The answer—24 percent—is comparable with that reported by others, and reinforces the conclusion that patients with that cytologic diagnosis should undergo surgery. Note that most of the carcinomas were the follicular variant subtype of papillary carcinoma, rather than a follicular or oncocytic (Hürthle-cell) carcinoma, which leads to the conclusion that not many cells in a nodule need have the characteristic nuclear features of papillary carcinoma to warrant the diagnosis of papillary carcinoma.

A third question is whether autoimmune thyroiditis is associated with an increased risk of thyroid carcinoma. The answer is no; there were no differences in the frequency of high serum antithyroid antibody concentrations, thyroid hypoechogenicity, or lymphocytic infiltration of the thyroid in the patients who had a carcinoma and those who had a benign nodule. When lymphocytic infiltra-tion was present, the nodule as well as the rest of the thyroid was nearly always involved. Might then the presence of thyroiditis in a nodule, whether it is a carcinoma or a benign nodule, alter its growth?

Robert D. Utiger, M.D.

Hypothyroidism is common in patients treated with amiodarone, usually occurring during the first months of treatment

Batcher EL, Tang XC, Singh BN, Singh SN, Reda DJ, Hershman JM, for the SAFE-T investigators. Thyroid function abnormalities during amiodarone therapy for persistent atrial fibrillation. Am J Med 2007;120:880-5.

SUMMARY

Background Hypothyroidism and hyperthyroidism are well-recognized adverse effects of amiodarone, but little is known about their relative frequency. In this study, serum thyrotropin (TSH) was measured prospectively at regular intervals in a large group of patients with atrial fibrillation who were treated with amiodarone, sotalol, or placebo.

Methods The study subjects were 612 patients (607 men, 5 women; mean age, 67 years) with persistent atrial fibrillation treated with warfarin who were randomly assigned to treatment with amiodarone, sotalol, or placebo. For this study, the sotalol and placebo groups were combined. After treatment for four weeks, those who still had atrial fibrillation were treated by electrical cardioversion. Patients in sinus rhythm continued their assigned treatment, except that warfarin was discontinued. Those who had persistent or recurrent atrial fibrillation and then were knowingly treated with amiodarone or sotalol were excluded from the study.

All patients were followed for at least one year. Cardiac rhythm was determined by weekly monitoring by telephone. Serum TSH (reference range, 0.35 to 4.5 mU/L) was measured at base line, after three and six months, and every six months thereafter (duration of follow-up not given). Serum thyroxine (T_4) was not measured. T_4 therapy was initiated at the discretion of the treating physician.

Results The base-line characteristics of the patients in the amiodarone and sotalol-placebo groups were similar (Table 1).

During therapy, there was no difference in the incidence of low serum TSH values between the two groups, but the incidence of high serum TSH values was higher in the amiodarone group (Table 2). The overall odds ratio for high serum TSH values in the amiodarone group, as compared with the sotalol-placebo group, was 4.5, and it was similar in subgroups based on age, diabetes, ischemic heart disease, and duration of atrial fibrillation.

Table 1. Base-Line Characteristics of Patients with Atrial Fibrillation in the Amiodarone and Sotalol-Placebo Groups.

	Amiodarone (n=247)	Sotalol-Placebo (n=365)
Age (yr)	67	67
Body–mass index (kg/m^2)	31	31
Diabetes mellitus	62 (25%)	90 (25%)
Ischemic heart disease	64 (26%)	88 (24%)
Serum TSH		
<0.35 mU/L	5 (2%)	3 (1%)
0.35 to 4.5 mU/L	231 (95%)	334 (94%)
>4.5 mU/L	7 (3%)	19 (5%)
T_4 therapy	7 (3%)	5 (1%)

Table 2. Incidence of Low and High Serum TSH Concentrations in the Amiodarone and Sotalol-Placebo Groups.*

Serum TSH	Amiodarone (n=247)	Sotalol-Placebo (n=299)
<0.35 mU/L	13 (5%)	7 (2%)
>4.5–10 mU/L	62 (25%)	19 (6%)**
>10 mU/L	12 (5%)	1 (0.3%)**

*Excluding patients with abnormal serum TSH values at base line and patients in the sotalol-placebo group later treated with amiodarone.
**P<0.01, as compared with the amiodarone group.

Among the 74 patients in the amiodarone group who had high serum TSH values during follow-up, the values were high at three months in 43 (58 percent) and six months in 56 (76 percent). Most of remaining cases were detected by one year. Among the 20 patients who had high serum TSH values in the sotalol-placebo group, the values were high at three months in 10 (50 percent) and at six months in 16 (80 percent). Patients treated with amiodarone and those with higher serum TSH values were more likely to be treated with T_4 during the study.

Conclusion Hypothyroidism, as manifested by high serum TSH concentrations, is common in patients with atrial fibrillation who are treated with amiodarone. It often occurs during the first months of treatment, but is unrelated to other characteristics of the patients.

COMMENTARY

The patients in this study were defined as having subclinical hypothyroidism if their serum TSH concentrations were >4.5 to 10 mU/L and overt hypothyroidism if the concentrations were >10 mU/L. Serum free T_4 was not measured, so the incidence of overt hypothyroidism, as usually defined (high serum TSH and low serum free T_4 concentrations), is not known, but it is likely that nearly all of the patients would have had subclinical hypothyroidism.

Whether the physicians (presumably cardiologists) caring for these patients were informed of the serum TSH values or advised to take action is not described, but their actions were conservative. At 6 and 12 months, only 22 (30 percent) and 39 (53 percent), respectively, of the 74 patients with high serum TSH values in the amiodarone group, mostly patients with serum TSH values >10 mU/L, and none of the patients in the sotalol-placebo group, were taking T_4. Perhaps the serum TSH elevations were not confirmed locally, there were no clinical manifestations of hypothyroidism (as is likely), or the physicians were reluctant to give T_4 for fear of recurrent atrial fibrillation or other cardiac problems.

None of the above should be taken to mean that serum TSH should not be measured regularly—and indefinitely—in patients taking amiodarone. It can cause clinically important hypothyroidism and hyperthyroidism, and the latter is especially likely to occur after several years—hence the need for indefinite monitoring.

Robert D. Utiger, M.D.

Triiodothyronine replacement does not alter the hemodynamic, metabolic, and hormonal responses to coronary artery surgery

Spratt DI, Frohnauer M, Cyr-Alves H, Kramer RS, Lucas FL, Morton JR, Cox DF, Becker K, Devlin JT. Physiological effects of nonthyroidal illness syndrome in patients after cardiac surgery. Am J Physiol Endocrinol Metab 2007;293:E310-5.

SUMMARY

Background The most common abnormality of thyroid function in patients with nonthyroidal illness is a decrease in extrathyroidal conversion of thyroxine (T_4) to triiodothyronine (T_3) and therefore a fall in serum T_3 concentrations. There is limited evidence that this fall may be a beneficial adaptation to illness. In this study, the effect of T_3 replacement on cardiovascular function and protein catabolism in patients undergoing coronary artery surgery was determined.

Methods The study subjects were 59 patients (7 women, 52 men; mean age, 62 years) with coronary artery disease who underwent elective coronary-artery bypass grafting. All were ambulatory, and their preoperative left ventricular ejection fraction was ≥40 percent. They were randomly assigned to receive T_3, given as an intravenous bolus dose of 0.2 μg/kg at the time of cross-clamp removal after completion of the grafting procedure, followed by intravenous infusion of 0.033 μg/kg per hour for 24 hours, or placebo. The following were measured preoperatively and one or more times for 36 hours postoperatively: serum T_3 and thyrotropin (TSH); cardiac index, systemic vascular resistance, mixed venous oxygen saturation, and heart rate; and protein catabolism, measured as urinary nitrogen excretion and C-13-leucine flux in 10 patients in each group.

Results The mean serum T_3 concentration fell from 150 ng/dl (2.3 nmol/L) to 50 ng/dl (0.8 nmol/L) when the cross clamp was removed in both groups. Thereafter, it increased to 160 ng/dl (2.5 nmol/L) one hour after the bolus dose of T_3 was given and the T_3 infusion was started, and it ranged from 140 to 150 ng/dl (2.1 to 2.3 nmol/L) during the remainder of the 24-hour infusion. In contrast, the serum T_3 concentrations were 50 ng/dl (0.8 nmol/L) throughout the 24-hour infusion in the placebo group. At 36 hours, the values were 70 ng/dl (1.1 nmol/L) in both groups. (All serum T_3 values were extrapolated from Figure 1 of the paper and are therefore approximations.) The mean serum TSH concentrations were 0.6 and 1.8 mU/L, respectively, at the end of the infusions in the T_3 and placebo groups.

Postoperatively, there were no consistent differences in cardiac index, systemic vascular resistance, or mixed venous oxygen saturation in the two groups. There were similar increases in heart rate (22 beats/minute in the T_3 group and 19 beats/minute in the placebo group). There were no differences in the frequency of cardiac arrhythmias or the need for cardiovascular drugs in the two groups, and there were no episodes of cardiac ischemia in either group.

Urinary nitrogen excretion and C-13-leucine flux increased slightly after surgery, and the increments were similar in both groups.

Conclusion Serum T_3 concentrations fall substantially during elective cardiac surgery and remain low for at least 36 hours after surgery. Maintaining normal serum T_3 concentrations for 24 hours after surgery does not alter cardiovascular dynamics or protein metabolism during the immediate postoperative period.

COMMENTARY

Any important trauma or illness, and the accompanying caloric deprivation, results in a rapid fall in serum T_3 concentrations, caused primarily by decreased extrathyroidal conversion of T_4 to T_3. This low serum T_3 syndrome is the most common and probably the least important of the changes in pituitary–thyroid function that occur in patients with nonthyroidal illness. Specifically, it is distinct from the low serum T_4 and the low or normal serum TSH concentrations that occur in patients who have been severely ill for several days (1).

What is the role of T_3 replacement in patients with the low serum T_3 syndrome? As in this study, it is quite possible to maintain normal serum T_3 concentrations by giving small amounts of T_3. This is in itself interesting, because it provides strong evidence against three explanations for the fall in serum T_3 concentrations. One, the fall is due to a fall in serum T_3-binding proteins or the presence of inhibitors of binding in serum. Two, the fall is due to rapid T_3 clearance. Three, the fall is a technical artifact of measurement of serum T_3. If any of these were true, administration of T_3 would not promptly raise serum T_3 concentrations to normal.

The T_3 replacement had no effect on nitrogen excretion or leucine flux, indicating that the fall in serum T_3 does not protect against the increase in protein catabolism that accompanies acute illness. This is interesting, since an argument against T_3 administration is that it would increase nitrogen loss, and hence prevent the (teleologically implied) protein-saving effect of the fall in serum T_3 concentrations.

Other studies have suggested that there is either no effect or possible benefits of T_3 replacement in cardiac-surgery patients. The benefits have included a small increment in cardiac output, decreased incidence of atrial fibrillation, and improved fluid balance (2). In short, T_3 replacement may have a role in supporting high-risk cardiac-surgery patients.

Low serum T_3 concentrations are only one component of the nonthyroidal illness syndrome. It should not be inferred that these minimal effects of T_3 replacement apply to patients who are more seriously and chronically ill and have widespread abnormalities of pituitary–thyroid function.

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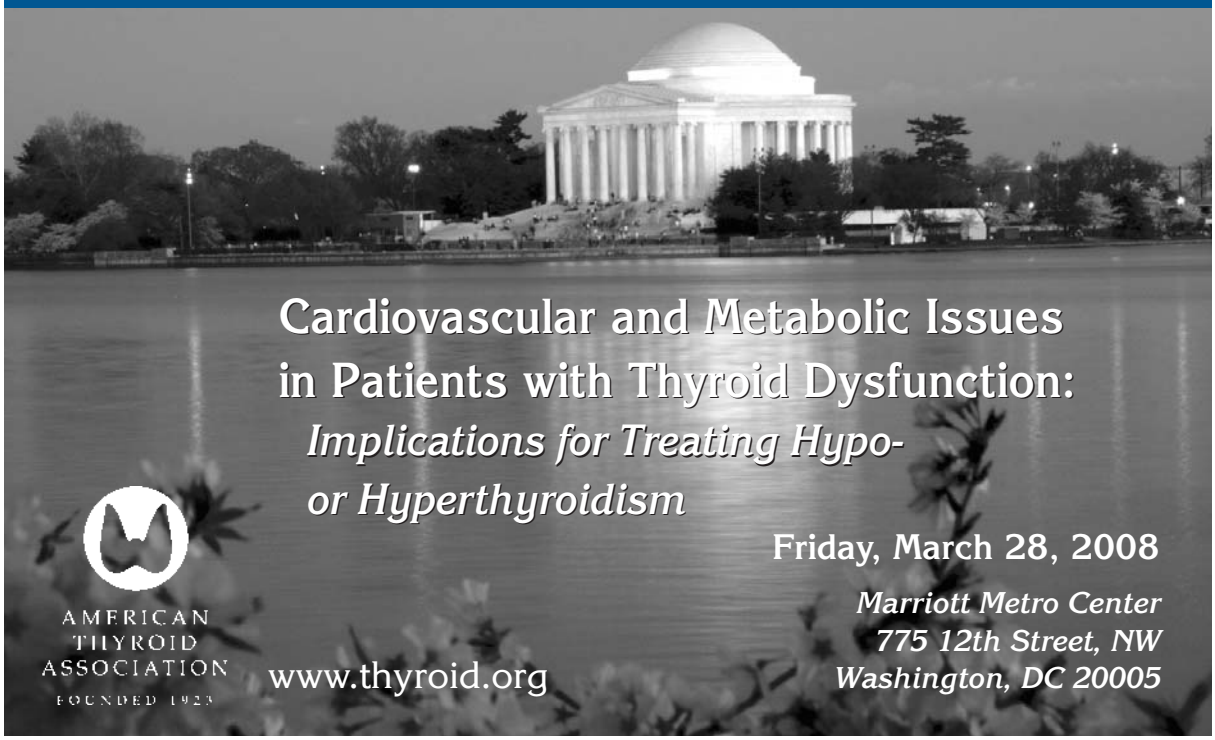

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