CLINICAL THYROIDOLOGY

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

Designed By
Karen Durland
Email: kdurland@mindspring.com

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Call for Abstracts

78th Annual Meeting of the American Thyroid Association

October 4–7, 2007
The Sheraton New York
New York, New York
www.thyroid.org

Deadlines

- Regular call: Site closes — Wednesday, May 30, 2007
- Short call: Site opens — Wednesday, August 15, 2007
  Site closes — Thursday, August 30, 2007

General Policies and Information

- Authors of accepted posters are required to be present during the assigned poster sessions.
- Scientific materials presented at the ATA Annual Meeting must not have been submitted for publication at the time of abstract submission or presented at a scientific meeting before the 78th Annual Meeting of the ATA (local and regional meetings excluded).
- All abstracts must be filed electronically via the American Thyroid Association website (www.thyroid.org). Submissions will not be accepted by fax or mail.
- All materials must arrive on or before the abstract deadlines noted above.
- Authorship on multiple abstracts is permitted.

Regular Abstracts

- Regular Abstracts submitted by the May 30 deadline will, with rare exceptions, be accepted for publication in the proceedings of the meeting and presentation as either a 10-minute oral talk or a poster.
- Notification of acceptance for Regular Abstracts will be e-mailed to the corresponding author before June 30, 2007.

Short Call Abstracts

- Short Call Abstracts should represent the very latest in thyroid-related research.
- Only five Short Call Abstracts will be selected for 10-minute oral presentations. Acceptance notices for those selected for oral and poster presentations will be e-mailed on or before September 5, 2007.
- The remaining accepted Short Call submissions will be presented at the meeting in a special section of posters.

Subclinical thyroid dysfunction is associated with socioeconomic deprivation but not nonthyroidal disorders in elderly subjects

Wilson S, Parle JV, Roberts LM, Roalfe AK, Hobbs FD, Clark P, Sheppard MC, Gammage MD, Pattison HM, Franklyn JA, on behalf on the Birmingham Elderly Thyroid Study Team. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community-based cross-sectional survey. J Clin Endocrinol Metab 2006;91:4809-16.

SUMMARY

Background The frequency of thyroid dysfunction increases with age, but the reasons for the increase are not clear. This study was done to determine the frequency of overt and subclinical thyroid dysfunction and to identify other health and socioeconomic factors associated with thyroid dysfunction in a cohort of elderly people.

Methods The study subjects were 5872 subjects (2980 women, 2892 men) aged 65 years or more (mean, 73) who attended family practices in the Birmingham (United Kingdom) area. They represented 36 percent of the people invited to participate. Subjects with a history of thyroid disease or who were taking thyroxine (T_4) were excluded.

The subjects were examined by a research nurse. Information about current medical diagnoses was obtained and the Index of Medical Deprivation score was determined; this index is based on place of residence and includes seven domains of deprivation (income, employment, health deprivation and disability, education and training, housing and services, crime, and living conditions). Serum thyrotropin (TSH) and free T_4 were measured in all subjects, and serum free triiodothyronine (T_3) was measured in those with low serum TSH values.

Results Among the 5872 subjects, 5538 (94.3 percent) were euthyroid, with normal serum TSH concentrations (median, 1.6 mU/L), 15 (0.2 percent) had overt hyperthyroidism, 128 (2.2 percent) had subclinical hyperthyroidism, 168 (2.9 percent) had subclinical hypothyroidism, and 23 (0.4 percent) had overt hypothyroidism. The frequency of these disorders was similar in women and men, except that subclinical hypothyroidism was more frequent in women (3.6 vs. 2.1 percent).

The deprivation score was slightly higher (more deprived) in the subjects with subclinical hyperthyroidism and lower (less deprived) in those with subclinical hypothyroidism, as compared with the euthyroid subjects (Table). These associations persisted after adjustment for age and nonthyroidal disorders.

Table. Deprivation Scores and Major Nonthyroidal Disorders in Euthyroid Subjects and Subjects with Subclinical Thyroid Dysfunction.

	Subclinical Hyperthyroidism (n=128)	Euthyroid (n=5538)	Subclinical Hypothyroidism (n=168)
Deprivation index			
Quartile 1	10%	20%	21%
Quartile 2	19%	19%	24%
Quartile 3	37%	33%	32%
Quartile 4	34%	28%	23%
Major diagnoses			
Hypertension	44%	47%	46%
Neurologic disorder	2%	1%	2%
Psychiatric disorder	6%	4%	7%
Rheumatic disorder	2%	2%	2%
Vascular disorder	15%	13%	11%

There was little difference in the frequency of 10 nonthyroidal disorders (data for five are shown in the table) in the subjects with subclinical hyperthyroidism or subclinical hypothyroidism and the euthyroid subjects.

Conclusion Among elderly subjects, subclinical hyperthyroidism is associated with greater socioeconomic deprivation and subclinical hypothyroidism with less socioeconomic deprivation, as compared with those with normal thyroid function.

COMMENTARY

Concern about adverse health events in patients with subclinical thyroid dysfunction has led some professional societies to recommend population-based screening of adults for thyroid disease. However, there is no evidence that there are any benefits of treatment in those found by screening to have thyroid disease. Consequently, two independent panels of thyroidologists and experts in related fields recommended against population-based screening of older people and suggested assessment of thyroid function only in patients with appropriate clinical indications (1,2).

Assuming that treatments for subclinical thyroid dysfunction are beneficial and safe, identifying people at increased risk might make screening paradigms more efficient and cost-effective. In this survey, subclinical hyperthyroidism was associated with more socioeconomic deprivation and subclinical hypothyroidism was associated with less socioeconomic deprivation. How variations in socioeconomic deprivation might relate to subclinical thyroid dysfunction is not at all clear. Limiting screening to older women is feasible, limiting it according to socio-economic status does not seem feasible, and limiting it to people with particular nonthyroidal disorders will not be more rewarding.

Because screening for thyroid dysfunction mostly identifies people with subclinical thyroid disease, mostly subclinical hypothyroidism, it cannot be justified unless it can be demonstrated that it is associated with an increased risk for adverse health events. Nevertheless, once identified, many patients with subclinical hypothyroidism are treated with T_4. The benefit/risk ratio of T_4 therapy in these patients is not known, but it is known that the rates of undertreatment and over-treatment of hypothyroidism are high, even though initiating and monitoring treatment with T_4 should be straightforward.

Martin I. Surks, M.D.
Montefiore Hospital, New York, NY

References

1. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease. Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.

2. Medicare coverage of routine screening for thyroid dysfunction. Washington, DC, Institute of Medicine, The National Academies Press. Accessed 3/9/07 at http://www.iom.edu/CMS/3809/4669/5921.aspx.

Cardiovascular symptoms and cardiac rate and rhythm abnormalities improve with treatment in patients with hyperthyroidism

Osman F, Franklyn JA, Holder RL, Sheppard MC, Gammage MD. Cardiovascular manifestations of hyperthyroidism before and after antithyroid therapy: a matched case-control study. J Am Coll Cardiol 2007;49:71-81.

SUMMARY

Background Hyperthyroidism has multiple effects on cardiovascular function. In this study, cardiovascular symptoms and function were assessed in patients with overt hyperthyroidism and then during or after treatment when they had subclinical hyperthyroidism and when they were euthyroid.

Methods The study subjects were 393 patients with overt hyperthyroidism and 393 age- and sex-matched control subjects. There were 312 women and 81 men in each group, and the groups were similar in age (mean, 49 years). All the patients had high serum free thyroxine (T_4) and undetectable serum thyrotropin (TSH) concentrations. The cause of the hyperthyroidism was Graves' disease in 147 patients (38 percent), nodular goiter in 88 (22 percent), and indeterminate in 158 (40 percent). Fifteen patients (4 percent) were treated with radioiodine, 160 (41 percent) with an antithyroid drug, and 218 (55 percent) with both.

All the patients were studied at base line, and 317 were studied again during or after treatment. At the time of the second study, 110 patients had subclinical hyperthyroidism (mean interval, 27 weeks) and 207 were euthyroid (mean interval, 37 weeks). The control subjects were studied once. Each study consisted of a systematic evaluation of cardiovascular symptoms and signs, electrocardiography (ECG), and usually 24-hour Holter monitoring.

Results More patients than control subjects had symptoms and signs of cardiovascular dysfunction (Table 1). The frequency of palpitation and cough was higher in the 110 patients studied when they had subclinical hyperthyroidism than in the matched control subjects and in the 207 patients studied when they were euthyroid than in their matched control subjects.

Table 1. Cardiovascular Findings in Patients with Hyperthyroidism and Control Subjects.

	Patients (n=393)	Control Subjects (n=393)
Palpitations	288 (73%)	79 (20%)*
Chest pain	97 (25%)	42 (11%)*
Dyspnea	236 (60%)	53 (14%)*
Cough	137 (35%)	45 (12%)*
Cardiac murmur	59 (15%)	21 (5%)*

*P<0.01, as compared with the patients.

The resting pulse rate and several other hemodynamic, ECG, and 24-hour monitoring results were higher or more frequent in the patients with hyperthyroidism (Table 2). As compared with the control subjects, most of the symptoms and some of the hemodynamic and monitoring abnormalities were no longer present in the patients with subclinical hyperthyroidism, and there were no differences in those studied when they were euthyroid.

Table 2. Hemodynamic, Electrocardiographic, and Monitoring Findings in Patients with Hyperthyroidism and Control Subjects.

	Patients (n=392)	Control Subjects (n=392)
Resting pulse rate (beats/min)	82	73*
Supine systolic blood pressure (mm Hg)	137	129*
Atrial fibrillation (ECG)	24 (6%)	3 (1%)*
24-hour monitoring (n=311)		
Minimum heart rate (beats/min)	60	54*
Maximum heart rate (beats/min)	128	122*
Atrial fibrillation	22 (7%)	4 (1%)*
>240 ventricular ectopic beats/24 hr	29 (9%)	26 (8%)
>240 atrial ectopic beats/24 hr	16 (5%)	14 (5%)
Supraventicular tachycardia	3 (1%)	3 (1%)

P<0.01, as compared with the patients.

Conclusion Some cardiovascular symptoms and heart rate abnormalities are more common in patients with hyperthyroidism than in age- and sex-matched control subjects. The abnormalities become progressively less frequent with transition from overt hyperthyroidism to subclinical hyperthyroidism to normal thyroid function.

COMMENTARY

Atrial fibrillation is probably the most worrisome effect of hyperthyroidism, because of its symptoms and the possibility of congestive heart failure and cerebral and other embolism, and it is the most difficult to reverse. Overall, there were 29 patients with atrial fibrillation in this study; it was of new-onset in 21 (5 percent), and among them it was persistent in 15 and paroxysmal in 6. As compared with the other patients, those who had atrial fibrillation were older and were more likely to have a history of cardiovascular disease, including congestive heart failure. All were treated with warfarin or aspirin, and many were treated with other drugs or electrical cardioversion. At last follow-up, 11 patients no longer had atrial fibrillation, but in only 5 was reversion to a normal rhythm spontaneous.

The persistence of some cardiovascular symptoms and hemodynamic and monitoring abnormalities when the patients had subclinical hyperthyroidism should not be taken to mean that the frequency of the abnormalities would be similar in patients with spontaneously occurring subclinical hyperthyroidism. The patients with subclinical hyperthyroidism in this study initially had overt hyperthyroidism, and they may still have had it not long before being studied, because their serum free T_4 concentrations were near the upper limit of normal and their serum TSH concentrations were still undetectable, not just low, when they were studied. These findings suggest that their serum free T_4 concentrations had not been normal for long, and also that treatment was conservative, since this was 27 weeks after radioiodine treatment was given or an antithyroid drug was started.

Robert D. Utiger, M.D.

Discordant changes in serum thyrotropin-receptor and antithyroid peroxidase antibodies in patients with hyperthyroidism caused by Graves' disease

Guilhem I, Massart C, Poirier JY, Maugendre D. Differential evolution of thyroid peroxidase and thyrotropin receptor antibodies in Graves' disease: thyroid peroxidase activity reverts to pretreatment level after carbimazole withdrawal. Thyroid 2006;16:1041-5.

SUMMARY

Background Patients with hyperthyroidism caused by Graves' disease characteristically have high serum concentrations of both thyrotropin receptor (TSHR)-stimulating and antithyroid peroxidase (anti-TPO) antibodies. In this study, serum TSHR-stimulating and anti-TPO antibodies were measured during and after antithyroid drug therapy in patients with Graves' hyperthyroidism to determine whether their production differed.

Methods Seventy-five patients (60 women, 15 men; mean age, 39 years [range, 19 to 64]) with new-onset Graves' hyperthyroidism were studied. The diagnosis was based on the presence of symptoms and signs of hyperthyroidism, diffuse goiter, ophthalmopathy, high serum free thyroxine (T_4) and free triiodothyronine (T_3) concentrations, and high thyroid radionuclide uptake.

The patients were treated with carbimazole, 60 mg daily, for 18 months. T_3 was added after the first month, and it was continued as needed to maintain normal thyroid status for 17 months. Both carbimazole and T_3 were then stopped, and the patients were followed for up to 3 years. They were evaluated clinically and had measurements of serum thyrotropin (TSH), free T_4, TSHR-stimulating antibodies (by bioassay; normal, <125 percent stimulation of thyroid-cell cyclic-AMP content), and anti-TPO antibodies (by radioimmunoassay; normal, <60 U/ml) at base line and repeatedly during treatment and as long as they remained euthyroid during the 3-year follow-up period.

Results Thirty-four of the 75 patients (45 percent) had recurrent hyperthyroidism during the 3-year post-treatment follow-up period, 13 in the first year, 14 in the second year, and 7 in the third year.

Serum TSHR-stimulating antibody concentrations were high in 74 patients (99 percent) at base line and 15 patients (20 percent) at the end of treatment, and the median value decreased from 359 to 111 percent. Two of the 15 patients (13 percent) with high values at that time remained euthyroid and 13 (87 percent) had recurrent hyperthyroidism, as compared with 39 (65 percent) and 21 (35 percent), respectively, of the 60 patients in whom the serum antibody values were not high. The median values in the patients who later had recurrent hyperthyroidism were higher than in those who remained euthyroid when treatment ended and thereafter.

Serum anti-TPO antibody concentrations were high in 64 patients (85 percent) at base line and 35 patients (47 percent) at the end of treatment, and the median value decreased from 816 to 91 U/ml. Eighteen of the 35 patients (51 percent) with high concentrations at that time remained euthyroid, as did 23 of the 40 patients (58 percent) of those with normal concentrations. The median values in the remission and recurrence groups were similarly high when treatment ended and one year later, and then increased two and three years later in both groups.

Conclusion In patients with hyperthyroidism caused by Graves' disease, serum anti-TPO antibody concentrations fall more than serum TSHR-stimulating antibody concentrations during antithyroid drug therapy and rise more after it is stopped, independent of recurrence of hyperthyroidism.

COMMENTARY

Does the natural history of Graves' hyperthyroidism, as manifested by production of TSHR-stimulating antibodies, differ from that of thyroid autoimmune disease in general, as manifested by production of anti-TPO antibodies? TSHR-stimulating antibodies are uniquely present in patients with Graves' hyperthyroidism. They are oligoclonal, but not monoclonal, they are heterogeneous in terms of their epitope specificity, and their epitope specificity may change with time and possibly therapy. Anti-TPO antibodies are present in high concentrations not only in patients with Graves' hyperthyroidism but also in those with all other types of autoimmune thyroid disease, for example, Hashimoto's thyroiditis and postpartum thyroiditis, whether they are euthyroid or have hyperthyroidism or hypothyroidism.

The production of TSHR-stimulating antibodies almost always decreases substantially during antithyroid drug therapy, as in this study. The decrease may be due to amelioration of hyperthyroidism (a similar fall occurs in patients treated by thyroidectomy) or an independent immunosuppressive effect of the drug. There may also be a qualitative change in the antibodies, because some patients have substantial serum concentrations of the antibodies, as measured in vitro, when antithyroid drug therapy is stopped, yet they remain euthyroid thereafter.

The production of anti-TPO antibodies also decreases during antithyroid drug therapy, but not as much as the production of TSHR-stimulating antibodies, whether considered as the percentage of patients who had normal values (53 vs. 80 percent) or median values (still high vs. normal), and the concentrations were less closely related to recurrences of hyperthyroidism after antithyroid drug therapy was stopped. In sum, the production of the two types of antibodies is discordant, indicating that thyroid autoimmunity persists even if Graves' disease does not.

Robert D. Utiger, M.D.

Hypothyroidism is more common after hyperthyroidism caused by amiodarone-induced thyroiditis than painful subacute thyroiditis

Bogazzi F, Dell'Unto E, Tanda ML, Tomisti L, Cosci C, Aghini-Lombardi F, Sardella C, Pinchera A, Bartalena L, Martino E. Long-term outcome of thyroid function after amiodarone-induced thyrotoxicosis, as compared to subacute thyroiditis. J Endocrinol Invest 2006;29:694-9.

SUMMARY

Background Hyperthyroidism caused by amiodarone-induced thyroiditis may last for several months, but little is known about the long-term outcome of the disorder. In this study, patients with hyperthyroidism caused by amiodarone-induced thyroiditis were followed for up to six years after cessation of prednisone therapy, and the results were compared with those of patients with painful subacute thyroiditis who were treated and followed similarly.

Methods The study subjects were 60 consecutive patients (13 women, 47 men; mean age, 67 years) with hyperthyroidism caused by amiodarone-induced thyroiditis and 60 consecutive patients (41 women, 19 men; mean age, 49 years) with painful subacute thyroiditis. The diagnosis in the former group was based on the presence of clinical and biochemical findings of hyperthyroidism, including high serum free thyroxine (T_4) and free triiodothyronine (T_3) and low thyrotropin (TSH) concentrations; and a normal-sized thyroid gland with hypovascularity, as determined by ultrasonography. Amiodarone was stopped in all the patients. The diagnosis of painful subacute thyroiditis was based on the presence of anterior neck pain, with or without fever, sore throat, and upper airway symptoms; a high erythrocyte sedimentation rate; high serum free T_4 and free T_3 and low serum TSH concentrations; and thyroid hypovasularity.

All patients in both groups were treated with prednisone; the initial dose was 30 mg daily, and it was progressively reduced and stopped in three months. Hyperthyroidism was considered cured when serum free T_4 and free T_3 concentrations were normal. The patients were followed periodically thereafter; the mean duration of follow-up was 38 months (range, 6 to 72) in the amiodarone-induced thyroiditis group and 40 months (range, 9 to 76) in the painful subacute thyroiditis group. Hypothyroidism was considered permanent when a patient's serum TSH concentration was high and free T_4 concentration was low on three consecutive occasions at least six months after prednisone was stopped.

Results At the time of diagnosis, the patients with hyperthyroidism caused by amiodarone had higher serum free T_4 and free T_3 concentrations than the patients with painful subacute thyroiditis, their thyroid glands were bigger, and their urinary iodine excretion was higher (Table).

Table. Characteristics of Patients with Hyperthyroidism Caused by Amiodarone-Induced Thyroiditis and Painful Subacute Thyroiditis.

	Amiodarone-Induced Thyroiditis	Painful Subacute Thyroiditis
Serum free T_4 (ng/dl)	3.7	2.3
Serum free T_3 (ng/dl)	1.0	0.7
Thyroid volume (ml)	16	12
Urine iodine (μg/L)	4455	79

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

All patients were euthyroid 10 to 150 days after the initiation of prednisone, but the mean (±SD) time to euthyroidism was longer in the amiodarone group (43±41 days) than in the painful subacute thyroiditis group (23±9 days, $P<0.01$). Subsequently, permanent hypothyroidism occurred in 10 patients (17 percent) in the amiodarone group and 3 patients (5 percent) in the painful subacute thyroiditis group. The interval from euthyroidism to hypothyroidism was longer in the amiodarone group (15 vs. 10 months).

The patients in the amiodarone group who had hypothyroidism did not differ from those who remained euthyroid with respect to the ratio of women to men, age, base-line serum free T_4 and free T_3 concentrations, cumulative dose and duration of amiodarone therapy, or time to disappearance of hyperthyroidism during prednisone therapy.

Conclusion Permanent hypothyroidism is more common after hyperthyroidism caused by amiodarone-induced thyroiditis than that caused by painful subacute thyroiditis.

COMMENTARY

The criteria for the diagnosis of hyperthyroidism caused by amiodarone-induced thyroiditis in this study were those generally accepted as defining the disorder, and the response to treatment with prednisone is taken as confirmation that the patients' hyperthyroidism was indeed caused by thyroid inflammation. It is likely that hyperthyroidism resolves with time alone in some if not most patients, but it is likely to take longer, based on studies in which prednisone proved more rapidly effective than other therapy.

The occurrence of permanent hypothyroidism after thyroiditis is not unexpected, but why should it be more common after amiodarone-induced thyroiditis than after painful subacute thyroiditis? One possibility is that amiodarone-induced thyroiditis is more destructive, even when prednisone is given. But if that is true, why should it take so long (an average of 15 months) for hypothyroidism to develop? Another possibility is that the iodide excess resulting from amiodarone therapy in the months before the onset of thyroiditis may have increased the intrathyroidal stores of T_4 and T_3, thus allowing not only more prolonged hyperthyroidism but also a more prolonged period of normal thyroid secretion before the stores were exhausted. Alternatively, amiodarone, which is cleared very slowly, causes some TSH-independent T_4 and T_3 synthesis that is not readily inhibited by prednisone, thus accounting not only for the more prolonged phase of hyperthyroidism, but also for the maintenance of normal thyroid secretion before the toxic effects of the drug result in hypothyroidism.

Robert D. Utiger, M.D.

The antitumor drug sunitinib can cause hypothyroidism

Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH, Morgan JA, Dychter SS, Larsen PR, Demetri GD, Alexander EK. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 2006;145:660-4.

SUMMARY

Background Many tumors have constitutively activated cellular receptors that have tyrosine kinase activity, which results in activation of intracellular signaling pathways that contribute to tumor growth. Sunitinib is a tyrosine kinase inhibitor that has proven effective in patients with gastrointestinal stromal tumors and renal-cell carcinoma. After two patients with gastrointestinal stromal tumors treated with sunitinib were found to have hypothyroidism, thyroid function was assessed regularly in a cohort of patients with this tumor being treated with sunitinib.

Methods The study subjects were 42 patients with gastrointestinal stromal tumors who had normal base-line serum thyrotropin (TSH) concentrations. The patients were treated with sunitinib in cycles in which they were given 50 mg of the drug daily for two or four weeks followed by two weeks of no therapy. Initially, serum TSH was measured irregularly, but later it was measured at the start of each treatment cycle. The median duration of sunitinib therapy in these 42 patients was 37 weeks (range, 10 to 167). Another 27 patients were excluded because they had preexisting thyroid dysfunction, serum TSH was not measured before the initiation of sunitinib, or sunitinib was given for only one or two cycles. Patients with high serum TSH concentrations were further evaluated, and some were treated with thyroxine (T_4).

Results During treatment, 15 of the 42 patients (36 percent) had hypothyroidism, as manifested by persistently high (not defined) serum TSH concentrations (serum T_4 values are not given). The mean base-line serum TSH concentration in these 15 patients was 2.1 mU/L (range, 0.7 to 4.6) and the maximum concentration was 63.9 mU/L (range, 7.2 to 288). Six patients (40 percent) had serum TSH concentrations between 5.0 and 20 mU/L and 9 (60 percent) had concentrations >20 mU/mL. In these 15 patients, the mean duration of sunitinib therapy was 104 weeks (range, 17 to 167). The mean time to a persistently high serum TSH concentration was 50 weeks (range, 12 to 94). The likelihood of hypothyroidism increased with duration of therapy. Among 22 patients treated for 36 weeks, 4 (18 percent) had hypothyroidism, as compared with 5 of 17 (29 percent) treated for 52 weeks and 9 of 10 (90 percent) treated for more than 96 weeks. The functional status of the patients with hypothyroidism, as assessed by standardized oncology clinical assessment, was similar to that of the patients with normal thyroid function; hypothyroid symptoms were not assessed.

Six of the 15 patients with hypothyroidism (40 percent) had low serum TSH concentrations on one or more occasions before having high concentrations. Thyroid ultrasonography in 2 patients with hypothyroidism revealed little thyroid tissue, and serum antithyroid peroxidase concentrations were normal in the 2 patients in whom they were measured. Twelve patients with serum TSH concentrations >10 mU/L who were treated with T_4 had persistently high values for 4 to 117 weeks (median, 17) (whether sunitinib was continued or stopped is not stated).

Among the 27 patients who did not have persistent hypothyroidism, 4 (15 percent) had low serum TSH concentrations, but stopped the drug and were not studied again. Seven (26 percent) had one or more serum TSH values between 5.0 and 7.0 mU/L but later had normal values.

Conclusion Sunitinib can cause hypothyroidism in patients with gastrointestinal stromal tumors.

COMMENTARY

It seems clear that sunitinib causes hypothyroidism in a substantial proportion of patients. Its onset is dependent on the duration of treatment; it is preceded by hyperthyroidism, at least as manifested by low serum TSH concentrations; it is not associated with goiter or high serum antithyroid antibody concentrations; and it is probably permanent in most patients. The evidence supporting these statements is in some instances sparse, but is presumed to be representative. Most patients received the same daily dose of sunitinib, but the duration of drug treatment during each cycle varied, and whether patients who received the drug for four weeks per cycle were more likely to have hypothyroidism than those who received it for two weeks per cycle is not stated.

How might sunitinib cause hypothyroidism? One possibility is that it inhibits one of the steps of thyroid hormonogenesis, but then there should be no transient hyperthyroidism and hypothyroidism should be accompanied by goiter and should not be permanent. Another is that it causes atrophic autoimmune thyroiditis, but then there should be no transient hyperthyroidism and serum antithyroid peroxidase antibody concentrations should be high. More likely, hypothyroidism results from a direct effect of the drug to injure and ultimately destroy the thyroid. This could be the result of inhibition of the tyrosine kinase activity of some intracellular signaling system, leading to inhibition of a pathway that maintains thyroid follicular function and integrity, or alternatively to stimulation of a pathway that causes thyroid follicular injury and death.

Drugs classified as tyrosine kinase inhibitors were developed to inhibit the tyrosine kinase activity of specific receptor or nonreceptor molecules, but it is clear that many of them, including sunitinib, inhibit multiple kinases, and they probably have other actions as well (1). Further studies of the thyroidal actions of sunitinib may provide insight into the factors that serve to maintain the integrity of the thyroid and also lead to a new way to destroy thyroid tissue.

Robert D. Utiger, M.D.

Reference

1. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med 2005;353:172-87.

Central hypothyroidism can occur during growth hormone therapy in patients with hypopituitarism

Agha A, Walker D, Perry L, Drake WM, Chew SL, Jenkins PJ, Grossman AB, Monson JP. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. Clin Endocrinol (Oxf) 2007;66:72-7.

SUMMARY

Background Treatment of patients who have hypopituitarism with growth hormone (GH) may result in small changes in serum thyroxine (T_4), triiodothyronine (T_3), or thyrotropin (TSH) concentrations. This study was done to determine the frequency of changes in pituitary–thyroid function in a large group of adults with hypopituitarism during GH treatment.

Methods The study subjects were 243 patients (148 women, 95 men; mean age, 47 years [range, 17 to 77]) with acquired GH deficiency caused by a pituitary adenoma (155 patients), craniopharyngioma (20 patients), other sellar masses (43 patients), and idiopathic hypopituitarism, brain tumors, and postpartum pituitary infarction (25 patients); 179 had undergone surgery and 171 radiotherapy. All had GH deficiency, as determined by peak serum GH concentrations <3 ng/ml in response to insulin-induced hypoglycemia or other stimuli. At base line, 159 patients (65 percent) had central hypothyroidism and 84 (35 percent) did not. All patients had been taking appropriate replacement therapy for three months before GH therapy was started.

The patients were treated with GH in doses that raised their initially low serum insulin-like growth factor I concentrations to the upper half of the age-adjusted normal range (median dose, 0.4 mg daily). Serum total T_4 or free T_4 (but not both), total T_3, and TSH were measured at base line and 3, 6, 9, and 12 months after the initiation of GH therapy. At 3 and 6 months, a diagnosis of hypothyroidism was made if the patient's serum total T_4 or free T_4 value was low and serum TSH was low or normal.

Results In the 84 patients who did not have central hypothyroidism and were not taking T_4 at base line (untreated group), the mean serum total T_4 or free T_4 values decreased slightly at three months, whereas serum total T_3 and TSH values did not change (Table). The serum total T_4 or free T_4 value was low at three months in 25 (30 percent) of these patients, and therefore they were treated with T_4. In the remaining 59 patients, the mean serum total T_4 value was slightly lower at six months, and 5 (6 percent) had hypothyroidism. Overall. 30 patients (36 percent) had hypothyroidism during the first six months of GH therapy.

Table. Mean Changes from Base Line in Serum Total T_4 or Free T_4, Total T_3, and TSH Concentrations during GH Replacement Therapy in Patients with Hypopituitarism.

	Total T_4 (μg/dl)	Free T_4 (ng/dl)	Total T_3 (ng/dl)	TSH (mU/L)
Untreated group				
3 months	–0.9 (n=33)*	–0.2 (n=51)*	+6 (n=84)	0 (n=84)
6 months	–0.7 (n=20)	–0.1 (n=39)	+5 (n=59)	–0.1 (n=59)
No. treated with T_4	15	15		
T_4-treated group				
3 months	–0.8 (n=76)*	–0.1 (n=83)	+6 (n=159)	
6 months	–0.5 (n=60)	–0.1 (n=76)	+2 (n=136)	
No. needing more T_4	19	6		

*P<0.02. To convert total T_4 and free T_4 values to nmol/L and pmol/L, respectively, multiply by 12.9; to convert T_3 values to nmol/L, multiply by 0.0154.

In the T_4-treated group, the mean serum total T_4 values decreased slightly at three months, but there were no changes in serum free T_4, total T_3, or TSH values (the latter were undetectable at all times). The serum total T_4 or free T_4 values decreased to below normal in 23 patients (14 percent), and therefore their dose of T_4 was raised.

In those patients who did not become hypothyroid or need more T_4 at 3 or 6 months, the serum total or free T_4, total T_3, and TSH values at 9 and 12 months were similar to those at base line.

Conclusion GH therapy in patients with hypopituitarism can cause central hypothyroidism, presumably by inhibiting TSH secretion.

COMMENTARY

GH replacement in adults with hypopituitarism has several effects on hypothalamic-pituitary-thyroid function. One is to reduce TSH and therefore thyroid secretion, sometimes sufficiently to cause central hypothyroidism. This probably occurs only in patients who already have some limitation of TSH secretion, and who therefore are more vulnerable to the inhibitory effect of GH therapy. This hypothesis is supported by the finding in this study that, among the 84 patients in the untreated group, hypothyroidism occurred during GH therapy in 26 of the 59 patients (44 percent) with multiple pituitary hormone deficiencies, but in only 4 of the 25 patients (16 percent) with isolated GH deficiency.

The most common abnormality of TSH secretion in patients with hypothalamic–pituitary disease is a decrease in the nocturnal surge of TSH secretion. This alone may not be sufficient to reduce 24-hour thyroid secretion to below normal, but any additional inhibition of TSH secretion caused by raising serum GH or insulin-like growth factor-I concentrations might well do so. Whether this inhibition is mediated by GH or insulin-like growth factor I is not known, but it likely involves an increase in hypothalamic secretion of somatostatin, which at least in pharmacologic quantities is known to inhibit TSH secretion.

GH replacement may also increase T_4 clearance, as manifested by the small fall in serum total T_4 or free T_4 concentrations in the T_4-treated patients. Some of this increase can be explained by an increase in extrathyroidal conversion of T_4 to T_3, but clearance by other pathways may also be increased.

As a practical matter, it is clear that thyroid function should be monitored regularly by measurements of serum free T_4 during the early months of GH therapy in patients with hypopituitarism.

Robert D. Utiger, M.D.

Hypothyroidism can alter cortisol metabolism resulting in apparent mineralocorticoid excess

Inagaki K, Otsuka F, Otani H, Sato C, Miyoshi T, Ogura T, Makino H. Apparent mineralocorticoid excess manifested in an elderly patient with hypothyroidism. Am J Hypertens 2007;20:104-7.

SUMMARY

Background Hypothyroidism is characterized by an increase in peripheral vascular resistance, and occasional patients have hypertension that is fully responsive to treatment with thyroxine (T_4). The clearance of aldosterone and other components of the renin–angiotensin system is slowed, but the overall function of the system is normal, even in those patients with hypertension. This report describes a patient with hypothyroidism and the syndrome of apparent mineralocorticoid excess (hypertension and hypokalemia) who was found to have a high ratio of cortisol to cortisone in serum indicative of a decrease in the activity of 17β-hydroxysteroid dehydrogenase type 2, thus increasing the mineralocorticoid activity of cortisol.

Case Report The patient was an 84-year-old woman with a history of hypertension and peripheral vascular disease who was referred for evaluation of increasing hypertension and hypokalemic alkalosis, fatigue, and edema. Her blood pressure was 180/80-90 mm Hg while taking candesartan. She had no family history of hypertension or renal tubular disease. Her serum sodium concentration was 144 mmol/L, potassium 2.6 mmol/L, chloride 100 mmol/L, and creatinine 0.9 mg/dl (79 μmol/L). Creatinine clearance was 42 ml/min, and urinary potassium excretion when she had hypokalemia was 25 mmol/day. Plasma renin activity was <0.1 ng/ml/hr and plasma aldosterone concentrations ranged from undetectable to 0.9 ng/dl (25 pmol/L). Plasma ACTH, cortisol, deoxycorticosterone, corticosterone, and catecholamine concentrations were normal. Adrenal imaging was normal. There was no history of licorice ingestion. The sequences of the exons of the 11β-hydroxysteroid dehydrogenase type 2 gene were normal.

The patient's serum thyrotropin (TSH) concentration was 109 mU/L and her serum free T_4 concentration was 0.4 ng/dl (5 pmol/L). Ultrasonography of the neck revealed an atrophic thyroid; tests for serum antithyroid peroxidase and antithyroglobulin antibodies were negative.

The ratio of cortisol to cortisone in serum was 10 to 12 (normal mean, 4.0). The patient was treated with spironolactone and potassium supplements for approximately two weeks, and T_4. She improved clinically, and her blood pressure decreased and her serum potassium increased. The improvement was maintained after the spironolactone and potassium supplements were stopped. Her serum cortisol: cortisone ratio gradually decreased to within the normal range, and her plasma renin activity and plasma aldosterone concentrations gradually increased to normal (approximately 0.4 ng/ml/hr and 7.5 ng/dl [207 pmol/L]).

Conclusion Hypothyroidism can result in a decrease in the activity of 11β-hydroxysteroid dehydrogenase type 2 that is sufficient to cause mineralocorticoid excess.

COMMENTARY

The evidence that this patient had mineralocorticoid excess is good, although it is not clear that other causes of renal potassium wasting, for example, surreptitious diuretic ingestion, were excluded, but that seems unlikely in an 84-year-old woman. The hypokalemia and other biochemical changes cannot be attributed to candesartan; it is an angiotensin-receptor antagonist that should if anything cause hyperkalemia and raise plasma renin activity.

Cortisol and cortisone are extensively interconverted in vivo by two 11β-hydroxysteroid dehydrogenases. 11β-Hydroxysteroid dehydrogenase type 1, primarily a hepatic enzyme, catalyzes the conversion of cortisone to cortisol, whereas 11β-hydroxysteroid dehydrogenase type 2, present in the kidneys and other mineralocorticoid target tissues, catalyzes the conversion of cortisol to cortisone, thereby protecting these tissues from the mineralocorticoid activity of cortisol. When the activity of 11β-hydroxysteroid dehydrogenase type 2 is decreased, as a result of mutation or inhibition (licorice), or is overwhelmed, as a result of a marked increase in cortisol secretion, there is mineralocorticoid excess (and concomitant inhibition of the renin–angiotensin–aldosterone system).

Patients with hypothyroidism have a high ratio of tetrahydrocortisol: tetrahydrocortisone in urine (1,2) as well as a high ratio of cortisol:cortisone in serum (this study). These changes are consistent with an increase in type 1 or a decrease in type 2 11β-hydroxysteroid dehydrogenase activity. Because the latter enzyme is present in the kidneys, a decrease in its activity would be more likely to raise intrarenal concentrations of cortisol to the level needed for it to exert mineralocorticoid actions.

Patients with T_4-sensitive hypertension are not unique (3), but patients like this seem to be. It is possible that the apparent mineralocorticoid excess was not the result of hypothyroidism alone, but instead the result of hypothyroidism plus some change in the mineralocorticoid receptor or the milieu within renal tubular cells that exaggerated the mineralocorticoid action of cortisol. The rarity of the changes, contrasted with the frequency of hypothyroidism, suggests that hypothyroidism alone was not the culprit.

Robert D. Utiger, M.D.

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Serum insulin-like growth factor I and its binding proteins increase in response to thyroxine in patients with hypothyroidism

Schmid C, Zwimpfer C, Brandle M, Krayenbuhl PA, Zapf J, Wiesli P. Effect of thyroxine replacement on serum IGF-I, IGFBP-3 and the acid-labile subunit in patients with hypothyroidism and hypopituitarism. Clin Endocrinol (Oxf) 2006;65: 706-11.

SUMMARY

Background Both thyroid hormone and growth hormone (GH) are needed for normal growth, and GH and insulin-like growth factor I (IGF-I) production and action are decreased in patients with hypothyroidism and hypopituitarism. In this study, serum IGF-I and the key IGF-I transport proteins acid-labile subunit (ALS) and insulin-like growth factor-binding protein 3 (IGFBP-3) were measured in patients with primary hypothyroidism and central hypothyroidism (hypopituitarism) before and during thyroxine (T_4) therapy.

Methods The study subjects were 28 patients with hypothyroidism (15 women, 13 men). Eighteen patients (mean age, 44 years) had primary hypothyroidism and 10 (mean age, 46 years) had central hypothyroidism. The causes of primary hypothyroidism were autoimmune thyroiditis (17 patients) and thyroidectomy (1 patient). Eight of the patients with central hypothyroidism had panhypopituitarism, and two had normal pituitary–adrenal function; the causes were pituitary adenoma (7 patients) and craniopharyngioma, germinoma, and congenital hypopituitarism (1 patient each).

Serum IGF-I, ALS, and IGFBP-3 were measured at base line and when the patients were euthyroid during treatment with T_4, this interval was 30±27 (mean±SD) weeks in the patients with primary hypothyroidism and 16±13 weeks in the patients with hypopituitarism. Serum IGF-I was measured by radioimmunoassay after removal of binding proteins, ALS by enzyme-linked immunoassay, and IGFBP-3 by immunoblot (normal values for these measurements are not given).

Results The mean serum TSH and free T_4 concentrations in the 18 patients with primary hypothyroidism were 267 mU/L and 0.3 ng/dl (4 pmol/L), respectively, at base line and 2.3 mU/L and 1.6 ng/dl (20 pmol/L), respectively, during T_4 therapy. Their serum IGF-I, ALS, and IGFBP-3 concentrations increased during T_4 therapy (Table).

Table. Mean Serum IGF-I, ALS, and IGFBP-3 Concentrations before and during T_4 Therapy in Patients with Primary Hypothyroidism and Central Hypothyroidism.

	Primary Hypothyroidism (n=18)	Central Hypothyroidism (n=10)
Serum IGF-I (μg/L)		
Base line	101	49
During T_4 therapy	158*	97*
Serum ALS (mg/L)		
Base line	12.6	7.8
During T_4 therapy	15.6*	11.0*
Serum IGFBP-3 (AU**)		
Base line	0.76	1.00
During T_4 therapy	1.00*	1.00

*P≤0.01, as compared with base line. **AU denotes arbitrary units.

The mean serum TSH and free T_4 concentrations in the patients with central hypothyroidism were 3.9 mU/L and 0.4 ng/dl (5 pmol/L), respectively, at base line; the latter was 1.2 ng/dl (16 pmol/L) during T_4 therapy. Their base line serum IGF-I and ALS concentrations were lower than in the patients with primary hypothyroidism, and they increased during T_4 therapy, but not to normal; serum IGFBP-3 did not change.

Conclusion Serum concentrations of IGF-I and ALS increase during T_4 therapy in patients with primary hypothyroidism and patients with central hypothyroidism (and GH deficiency), but serum IGFBP-3 increases only in the former.

COMMENTARY

There are six IGF binding proteins, but over 95 percent of the IGF-I in serum is bound to IGFBP-3, and the complexes of IGF-I and IFGBP-3 are in turn bound to the ALS. IGF-I, ALS, and IGFBP-3 are produced primarily, if not solely, in the liver, and their production is GH-dependent.

It is also in part T_4-dependent, in both the absence and presence of GH, and the extent of the interplay of T_4 and GH can be inferred from this study. Serum IGF-I and ALS concentrations were low and increased during T_4 therapy in patients with primary hypothyroidism. The concentrations were even lower in the patients with central hypothyroidism and GH deficiency, and did not rise during T_4 therapy to the values reached during T_4 therapy in the patients with primary hypothyroidism. Serum IGFBP-3 was T_4-sensitive only in the patients with primary hypothyroidism.

What about GH secretion? In patients with primary hypothyroidism, GH secretion in response to provocative stimuli may be impaired. More important, so is nocturnal GH secretion (1), although the action of exogenous GH to increase IGF-I production is normal (2). GH secretion was not measured in the patients with primary hypothyroidism in this study, but it is likely to have been more normal in them than in the patients with central hypothyroidism, both before and during T_4 therapy.

Taken together, these results seem to indicate that T_4 stimulates the secretion of GH, facilitates the action of GH to stimulate IGF-I, ALS, and IGFBP-3 production, and independently stimulates the production of IGF-I and ALS but not IGFBP-3.

Robert D. Utiger, M.D.

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The effect of thyroxine is greater when taken at bedtime

Bolk N, Visser TJ, Kalsbeek A, van Domburg RT, Berghout A. Effects of evening *vs* morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients. Clin Endocrinol (Oxf) 2007;66:43-8.

SUMMARY

Background Patients with hypothyroidism who are taking thyroxine (T_4) are often advised to take their daily dose 30 to 60 minutes before eating in the morning, because some foods reduce the absorption of T_4. This study was done to determine whether ingestion of T_4 at different times of the day resulted in different patterns of 24-hour serum thyroid hormone and thyrotropin (TSH) concentrations.

Methods The study subjects were 11 women (mean age, 48 years) with hypothyroidism who were taking T_4 (mean dose, 121 μg daily) either 30 minutes before breakfast or at bedtime. None was taking any medications known to interfere with T_4 absorption or clearance or had any gastrointestinal disease.

Most women were studied while they were taking their usual dose of T_4 30 minutes before breakfast and again after they had taken it at bedtime (2200 hours) for two months; the sequence was reversed in the others. For each study, blood samples for measurements of serum TSH, total T_4, free T_4, total triiodothyronine (T_3), albumin, and thyroxine-binding globulin (TBG) were obtained hourly via an indwelling catheter for 24 hours, during which time the women ate at 0730, 1230, and 1730 hours, were ambulatory during the day, and went to bed at 2200 hours. Vital signs were measured hourly and quality-of-life was assessed using a 20-question thyroid-disorder symptom score and the Short Form-36 questionnaire during both studies.

Results The mean hourly serum TSH values were considerably lower and the mean hourly serum free T_4 and total T_3 concentrations were slightly higher when T_4 was taken at bedtime than when it was taken in the morning (Table), but there were no differences in mean hourly serum total T_4, TBG, or albumin concentrations.

Table. Mean 24-Hour Serum TSH, Thyroid Hormone, and Protein Concentrations in Patients with Hypothyroidism Taking T_4 30 Minutes before Breakfast in the Morning and at Bedtime.

Serum	Morning	Bedtime
TSH (mU/L)	5.1	1.2*
Free T_4 (ng/dl)	1.3	1.5*
Total T_4 (μg/dl)	8.9	9.4
Total T_3 (ng/dl)	96	106*
Albumin (g/L)	37.2	38.2

*P<0.01.
To convert serum total and free T_4 values to nmol/L and pmol/L, respectively, multiply by 12.9; and to convert serum total T_3 values to nmol/L, multiply by 0.0154.

The 24-hour pattern of serum TSH concentrations, with higher values late in the evening and during the night and lower values during the day, was similar in both studies, despite the higher hourly values when T_4 was taken in the morning. The 24-hour patterns of serum total T_4, free T_4, total T_3, albumin, and TBG concentrations also were similar in the two studies, whether the mean 24-hour values were different (serum free T_4, total T_3) or similar (serum total T_4, albumin, TBG).

Serum free T_4 and total T_3 concentrations were slightly lower at all times when T_4 was taken in the morning. The overall mean 24-hour serum TSH concentrations were negatively correlated with the overall mean 24-hour serum free T_4 concentrations. There were no differences in vital signs or questionnaire responses during the two studies, except that the bodily pain subscore of the Short Form-36 was higher (more normal) during bedtime administration of T_4.

Conclusion Serum free T_4 and total T_3 concentrations are higher and serum TSH concentrations are lower when T_4 is taken at bedtime than early in the morning, suggesting that absorption of T_4 is better at night.

COMMENTARY

Normally, 60 to 80 percent of an oral dose of T_4 dose is absorbed, primarily in the jejunum and ileum (1). T_4 absorption is reduced by some drugs, gastrointestinal disorders, and concomitant food ingestion, none of which was a factor in this study, and by decreased gastric acidity (1). Conversely, T_4 absorption increases when gastric acid secretion increases. Basal gastric acid secretion is highest in the late evening and lowest in the morning. In addition, bowel motility is slower at night. These circadian differences in gastrointestinal function provide support the authors' hypothesis that increased absorption of T_4 accounts for the higher serum free T_4 and lower serum TSH concentrations when T_4 is taken in the evening rather than in the morning.

There are alternative explanations. One is that T_4 absorption is decreased when food is eaten 30 minutes after T_4 is taken (the morning study), but not when it is taken 4.5 hours after eating (the evening study), independent of gastric acidity. Other explanations are that the hepatic uptake and metabolism of T_4 are greater when it is taken in the morning, so less reaches the systemic circulation, or that its peripheral uptake and metabolism are greater in the morning, so it is cleared from the systemic circulation more rapidly. However, the clearance and metabolism of T_4 are slow and are unlikely to vary according to the time of T_4 ingestion.

Given that millions of people are taking T_4, we know remarkably little about its absorption and the factors that alter it. Bolk et al. have increased our knowledge of this topic, and their results are relevant to clinical practice. In the morning rush, many patients may have trouble remembering to take T_4, or they take it and eat very soon thereafter. The results of this study indicate that bedtime administration is fine, but if that change is made, the dose of T_4 may need to be reduced.

Mary H. Samuels, M.D.
Oregon Health Sciences University
Portland, OR

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Increasing serum thyrotropin concentrations are associated with increasing risk of thyroid carcinoma in patients with thyroid nodules

Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006;91:4295-301.

SUMMARY

Background Most thyroid nodules are benign, but a few are carcinomas. No clinical, biochemical, or imaging findings reliably identify those nodules that are carcinomas; this can be done only by cytologic evaluation of cells obtained by aspiration of the nodule. This study was done to reexamine the possibility that some clinical or biochemical factors might predict that a thyroid nodule was a carcinoma.

Methods The study subjects were 1500 euthyroid patients (1304 women, 196 men; mean age, 48 years) seen at a thyroid clinic in the United Kingdom. Based on palpation, 861 (58 percent) had a solitary nodule, 456 (30 percent) a multinodular goiter, and 183 (12 percent) a diffuse goiter. A respiratory flow-loop study was done in 697 patients who had symptoms of upper airway obstruction. Serum thyrotropin (TSH) was measured in 1183 patients.

All the patients underwent fine-needle aspiration of the thyroid. The dominant nodule was aspirated in patients with a multinodular goiter, and multiple areas were aspirated in those with a diffuse goiter. Cytologic findings were classified as inadequate, benign, follicular tumor, suspicious for carcinoma, and diagnostic of carcinoma. A second aspiration was done in 479 patients (32 percent) and additional aspirations were done in 177 patients (12 percent) in whom the aspirates were inadequate or the nodule later enlarged. Patients not operated on were followed for at least two years (mean, 10) to confirm the diagnosis of benign nodule.

Results The cytologic diagnosis was benign nodule in 1086 patients (72 percent), follicular tumor in 291 (20 percent), and suspicious or diagnostic of carcinoma in 30 (2 percent). The initial aspirate was inadequate in 257 patients (17 percent), and repeated aspirations were inadequate in 93 (6 percent); 33 of these 93 patients underwent surgery.

All 30 patients in whom the biopsy was suspicious or diagnostic of carcinoma, all 291 with a diagnosis of follicular tumor, 85 with upper airway obstruction, 31 with recurrent accumulation of cyst fluid, 33 with repeatedly inadequate aspirates, and 83 with cosmetic problems underwent surgery or open biopsy. Among these 553 patients, 120 (22 percent) had a thyroid carcinoma (8 percent of the entire cohort); 62 had papillary carcinoma, 31 follicular carcinoma, 13 Hürthle-cell carcinoma, and 14 medullary or anaplastic carcinoma or lymphoma.

Thyroid carcinoma was more common in men (12 vs. 8 percent) and in patients aged <30 years or ≥80 years (approximately 15 percent in these age groups vs. 7 percent in patients aged 30 to 79 years). Serum TSH, measured in 1183 patients, was abnormal in 209 (18 percent). The frequency of carcinoma was lowest in those with low serum TSH values and highest in those with high values (Table). In patients with normal serum TSH values, the frequency of carcinoma increased with increasing tertile of serum TSH.

Table. Frequency of Thyroid Carcinoma in Relation to Serum TSH Concentration in 1183 Patients with Thyroid Nodules or Goiter.

Serum TSH (mU/L)*	No.	No. with Carcinoma
<0.4	182	5 (3%)
0.4 to 0.9	322	9 (4%)
1.0 to 1.7	336	28 (8%)
1.8 to 5.5	316	39 (12%)
>5.5	27	8 (30%)

*Normal values, 0.4 to 5.5 mU/L.

Conclusion Among patients with thyroid nodules or goiter, higher serum TSH values are associated with a higher likelihood of carcinoma.

COMMENTARY

In this study of patients with three types of thyroid enlargement, as determined by palpation, the risk of thyroid carcinoma was increased in those with a solitary nodule, younger or older age, and increasing serum TSH concentrations. Among patients evaluated by ultrasonography, approximately 50 percent of those with a solitary nodule on physical examination have multiple nodules, and the risk of carcinoma is similar in those with single and those with multiple nodules. Furthermore, most patients in this study who had a diffuse goiter on palpation probably had a multinodular goiter.

The finding of a higher prevalence of thyroid carcinoma with increasing serum TSH values, even within the normal range, is an interesting observation. While it has long been recognized that the likelihood of carcinoma is low in patients with thyroid nodules who have low serum TSH values, a direct relationship between increasing serum TSH values in euthyroid patients and the prevalence of thyroid carcinoma has not been recognized previously.

TSH is a thyroid growth factor, but whether it is a thyroid carcinogenic factor is less clear. The frequency of both subclinical and overt hypothyroidism and of thyroid nodules increases with age, but the frequency of thyroid carcinoma does not. On the other hand, the frequency of autoimmune thyroiditis may be increased in patients with thyroid carcinoma (1), and it is also the most common cause of high serum TSH concentrations. Perhaps autoimmune thyroiditis, leading to gradual thyroid failure and progressively increasing serum TSH concentrations, increases the risk of carcinoma, given the thyroid growth and proliferative actions of TSH.

M. Regina Castro, M.D.
Mayo Clinic
Rochester, MN

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Ultrasonography of the neck may reveal thyroid nodules including carcinomas in patients with primary hyperparathyroidism

Ogawa T, Kammori M, Tsuji E, Kanauchi H, Kurabayashi R, Terada K, Mimura Y, Kaminishi M. Preoperative evaluation of thyroid pathology in patients with primary hyperparathyroidism. Thyroid 2007;17:59-62.

SUMMARY

Background Many patients with primary hyperparathyroidism are now treated by minimally invasive parathyroidectomy, with less attention paid to the possibility of concomitant thyroid nodular disease, including thyroid carcinoma, than if they were to undergo conventional bilateral neck exploration. In this study, patients with primary hyperparathyroidism were evaluated preoperatively by ultrasonography of the thyroid to determine the frequency of concomitant thyroid nodular disease.

Methods The study subjects were 85 patients (66 women, 19 men; mean age, 57 years) with primary hyperparathyroidism caused by one (83 patients) or two parathyroid adenomas (2 patients). Patients with primary parathyroid hyperplasia or multiple endocrine neoplasia were excluded. Among these 85 patients, 56 (66 percent) were asymptomatic, 18 (21 percent) had nephrolithiasis, and 8 (9 percent) had osteoporosis; 3 (3 percent) had palpable thyroid nodules and then were found to have hyperparathyroidism.

Ultrasonography and technetium-99m sestamibi imaging of the neck region were done in all patients. The sensitivity of these procedures for the detection of parathyroid adenomas was 93 and 91 percent, respectively. Thyroid nodules >5 mm were aspirated for cytologic analysis.

Twenty-one patients underwent bilateral neck exploration because they had coexisting thyroid nodules, two parathyroid adenomas, or the parathyroid adenoma was not located preoperatively. Patients who had thyroid carcinoma were treated by thyroid lobectomy if the carcinoma was <1 cm or thyroidectomy if it was larger; and most of these patients also underwent at least limited lymph node dissection. Benign thyroid nodules were resected.

Results Preoperative neck ultrasonography revealed thyroid nodules in 21 patients (25 percent). Nine patients (11 percent) proved to have malignant nodules, of which 7 were papillary carcinomas, 1 was a follicular carcinoma, and 1 was a lymphoma. The carcinomas ranged from 0.5 to 3.7 cm in longest dimension, and the lymphoma was 8.0 cm. Cervical lymph nodes were found to contain carcinoma in 3 of the 7 patients in whom nodes were resected. Twelve patients (14 percent) had benign nodules; 5 had a follicular adenoma and 7 a multinodular goiter. Whether any of the thyroid nodules were visualized on the sestamibi scans is not mentioned.

All diagnoses were confirmed by pathologic examination of the resected nodules, except in the patient with lymphoma, in whom the diagnosis was confirmed by open biopsy. This patient then received chemotherapy and external-beam radiation.

Conclusion In patients with primary hyperparathyroidism, preoperative ultrasonography of the neck may not only localize a parathyroid adenoma, but also may identify thyroid nodules that should be biopsied before parathyroid surgery is undertaken, because a different operation may be needed.

COMMENTARY

The frequency of benign thyroid nodules (14 percent) and thyroid carcinoma (11 percent) in these patients with primary hyperparathyroidism seems high, but may be explained by ascertainment bias. The paper by Ogawa et al. includes a table listing seven other similar studies of patients with primary hyperparathyroidism. They included from 65 to 2425 patients, and among them 4 to 31 (0.2 to 24 percent) had thyroid carcinoma. There is no plausible biologic basis for an association between primary hyperparathyroidism and papillary or follicular thyroid carcinoma.

Today, ultrasonography of the neck and sestamibi imaging to localize a parathyroid adenoma are done in most if not all patients with primary hyperparathyroidism in whom surgery is contemplated, so that if an adenoma is identified the patient can be treated by minimally invasive parathyroidectomy rather than conventional neck exploration. While the two procedures are equally satisfactory for identifying parathyroid adenomas, ultrasonography is superior for identifying thyroid nodules, but of course does not reliably distinguish between benign nodules and carcinomas. Sestamibi imaging is usually done 10 to 15 minutes and then again 120 minutes after administration of the radionuclide. Parathyroid adenomas are seen on both the early and late scans. The early scans reveal normal thyroid tissue, but the sestamibi rapidly washes out. Some benign thyroid nodules, including those that do not concentrate radioiodine, take up sestamibi, and it may not wash out; this pattern of increased uptake and lack of washout is even more common in thyroid carcinomas (1).

The possibility that patients with primary hyperparathyroidism may have thyroid nodular disease, and may need surgery for that, should always be kept in mind. When conventional neck exploration was done routinely, most sizable thyroid nodules would have been seen and resected or at least biopsied for frozen-section analysis. This may not have been optimal, given the limitations of frozen-section analysis, but still would spare some patients a second operation. When minimally invasive parathyroidectomy is contemplated, thyroid disease should be sought proactively.

Robert D. Utiger, M.D.

Reference

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Age at diagnosis, stage of disease, and extent of treatment predict survival in patients with medullary carcinoma of the thyroid

Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer 2006;107:2134-42.

SUMMARY

Background Medullary thyroid carcinoma is an uncommon type of thyroid carcinoma that has a poorer prognosis than the more common papillary and follicular carcinomas. This study was done to determine the prognosis of medullary carcinoma in a national cohort of patients with the disease.

Methods The study subjects were 1252 patients with histologically confirmed medullary carcinoma recorded in the database of the Surveillance, Epidemiology, and End Results (SEER) program between 1979 and 2002. This database contains demographic, clinical, pathologic, treatment, and outcome data for incident cases of all types of carcinoma in 13 urban and rural areas comprising 26 percent of the United States population. Patients who were not followed continuously were excluded. The database does not contain information regarding familial medullary carcinoma or biochemical data.

Results The 1252 patients included 746 women and 506 men. Their mean (±SD) age at the time of diagnosis was 50±18 years; 379 (30 percent) were aged <40 years, 586 (47 percent) were 40 to 65, and 287 (23 percent) were >65.

The carcinoma was 2.8±2.4 cm in longest dimension; it was localized to the thyroid in 595 patients (48 percent), it extended into the surrounding tissue in 437 (35 percent), and there were distant metastases in 166 (13 percent) (no staging information was available for 54 patients [4 percent]). Detailed information regarding lymph node metastases was available for 594 patients. Among them, 368 (62 percent) had none, 121 (20 percent) had ipsilateral node involvement, 49 (8 percent) had bilateral or contralateral node involvement, and 56 (10 percent) had mediastinal or other distant node involvement. The number of regional nodes examined averaged 12 (range, 0 to 90), and the mean number of nodes containing tumor was 4 (range, 0 to 75). One hundred sixty-three patients (13 percent) had more than one focus of medullary carcinoma in the thyroid.

Detailed information regarding treatment was available for 643 patients (51 percent). Ninety-one patients (14 percent) were treated by thyroid lobectomy, 235 (37 percent) by thyroidectomy, and 283 (44 percent) by thyroidectomy and limited or extensive node dissection; 34 patients (5 percent) were not operated on. External-beam radiation therapy was given to 148 patients (12 percent).

As of December 2003, 851 (68 percent) of the patients were alive. The mean survival time was 9 years (range, 0 to 30). Among patients with tumor confined to the thyroid, the 10-year survival rate was 96 percent, whereas it was 76 percent in patients with regional lymph node involvement and 40 percent in those with distant disease. On multivariate analysis, age at diagnosis, tumor stage, and extent of surgery were strong predictors of survival (Table).

Table. Clinical Characteristics and Treatment Variables Associated with Survival in Patients with Medullary Carcinoma, as Determined by Multivariate Analysis.

	Hazard Ratio (95% CI)	P Value
Age (y)		
<40	1.0	
40–65	2.4 (1.3-4.2)	0.004
>65	6.6 (3.7-11.6)	<0.001
Stage		
Localized	1.0	
Regional	2.7 (1.7-4.2)	<0.001
Distant	4.5 (2.6-7.7)	<0.001
Surgery		
None	1.0	
Thyroid lobectomy	0.5 (0.2-0.9)	0.04
Thyroidectomy, no node dissection	0.3 (0.2-0.6)	<0.001
Thyroidectomy, limited node dissection	0.2 (0.1-0.4)	<0.001
Thyroidectomy, extensive node dissection	0.2 (0.1-0.5)	<0.001

Conclusion Among patients with medullary carcinoma, younger age at the time of diagnosis, disease localized to the thyroid gland, and more extensive surgery are associated with improved long-term survival.

COMMENTARY

The strengths of this study include the large number of patients, the categorization of the extent of disease and of surgery, and the long follow-up. The pathologic diagnoses were not confirmed by central review, but it seems unlikely that many cases were misdiagnosed. A pathologic finding of note is the relative infrequency of multiple intrathyroidal foci of medullary carcinoma. Nothing is said about C (parafollicular)-cell hyperplasia, and therefore the opportunity to determine whether it is a precursor of sporadic medullary carcinoma, as it is a precursor of the familial forms of medullary carcinoma, was missed.

The authors note that there has been little change in the outcome of patients with medullary carcinoma for many years. There has been a tendency to perform more extensive lymph node dissections in these patients in recent years, but the long-term benefit of these more extensive operations is not established. The outcomes will be best when the tumors are identified while still confined to the thyroid or, better yet, before they are present at all, as in patients with germ line *ret* mutations who undergo thyroidectomy at an early age.

Robert D. Utiger, M.D.

Cellular atypia in aspirates of follicular tumors suggests the presence of carcinoma

Rago T, Di Coscio G, Basolo F, Scutari M, Elisei R, Berti P, Miccoli P, Romani R, Faviana P, Pinchera A, Vitti P. Combined clinical, thyroid ultrasound and cytological features help to predict thyroid malignancy in follicular and Hürthle cell thyroid lesions: results from a series of 505 consecutive patients. Clin Endocrinol (Oxf) 2007;66:13-20.

SUMMARY

Background Thyroid nodules that are papillary carcinomas can be reliably distinguished from those that are benign on the basis of the cytologic characteristics of cells obtained by fine-needle aspiration of the nodules. However, it has proven difficult to distinguish cytologically between follicular and Hürthle-cell carcinomas and follicular and Hürthle-cell adenomas. This study was done to reassess the value of cytologic details and also clinical and ultrasound findings in distinguishing between these types of tumors.

Methods The study group was 505 consecutive patients (398 women, 107 men; mean age, 45 years) with thyroid nodules that had been aspirated and for which the cytologic diagnosis was follicular or Hürthle-cell tumor. The ultrasound images of the nodules were analyzed by two examiners for echogenicity, margin sharpness, microcalcifications, and vascularity. The nodule aspirates were categorized by a single cytopathologist as follicular tumor without atypia (scant colloid, microfollicles, and increased cellularity, consisting of small cells with small nuclei containing diffusely distributed chromatin) and follicular tumor with atypia (absence of colloid, many nests of cells and isolated cells with large nuclei containing sparse chromatin and sometimes prominent nucleoli, with occasional mitoses). Aspirates containing oxyphilic cells with abundant dense or finely granular cytoplasm were considered to be Hürthle cells; they were subdivided according to the absence or presence of atypia as described above. Nodules with any of the nuclear features of papillary carcinoma, psammoma bodies, or pseudopapillary structures were excluded. All patients underwent thyroidectomy.

Results The cytologic diagnosis was follicular tumor in 426 nodules (84 percent) and Hürthle-cell tumor in 79 (16 percent). Among the 426 follicular tumors, 116 (27 percent) proved to be carcinomas, as did 9 of the 79 Hürthle-cell tumors (11 percent) (Table); overall, 125 of the 505 nodules (25 percent) were carcinomas. Most of the carcinomas were the follicular-variant subtype of papillary carcinoma. Among the 380 benign nodules, 288 (76 percent) were follicular adenomas (including 34 with <5-mm foci of papillary carcinoma within the adenoma), 52 (14 percent) were hyperplastic nodules, 36 (9 percent) were oxyphilic adenomas, and 4 (1 percent) were lymphocytic thyroiditis.

Table. Types and Numbers of Carcinomas among 505 Follicular or Hürthle-Cell Tumors with or without Cytologic Atypia.

	No.	Follicular Tumor		Hürthle-Cell Tumor	
		Atypia	No Atypia	Atypia	No Atypia
Papillary carcinoma					
Follicular variant	84	28	56	0	0
Classic variant	10	6	4	0	0
Others*	10	2	5	3	0
Follicular carcinoma	14	3	6	2	3
Other carcinoma**	7	1	5	1	0

*Oxyphilic and tall-cell subtypes of papillary carcinoma.
**Oxyphilic and poorly differentiated carcinoma.

Cytologic findings of atypia were seen in the aspirates of 101 nodules. Forty-six of these 101 nodules (46 percent) were carcinomas, as compared with 79 of the 404 nodules (20 percent) of the nodules with no atypia (P<0.001) (Table). Among the follicular tumors, 40 of 83 aspirates with atypia (48 percent) and 76 of 343 aspirates with no atypia (22 percent) were carcinomas. The comparable results for the Hürthle-cell tumors were 6 of 18 aspirates with atypia (33 percent) and 3 of 61 with no atypia (5 percent).

There was no association between age, sex, number of nodules, or nodule size and carcinoma. Among the ultrasound findings evaluated, only the presence of microcalcifications was associated with carcinoma.

Conclusion Approximately 25 percent of thyroid nodules for which the cytologic diagnosis is follicular or Hürthle-cell tumor prove to be carcinomas, and the likelihood of carcinoma is increased when there is cellular atypia in the aspirate of the nodule.

COMMENTARY

The categorization of aspirates of thyroid nodules as follicular or Hürthle-cell tumors in this study was restrictive, in that nodules that contained, in addition to the features of a follicular-patterned tumor, cells with any of the cytologic features of papillary carcinoma were excluded. Yet, 25 percent of the nodules were carcinomas, and most of them were the follicular-variant subtype of papillary carcinoma. This finding supports the widespread view that patients with nodules for which the cytologic diagnosis is follicular tumor should be advised to undergo thyroidectomy. The lower frequency of carcinoma among the Hürthle-cell tumors may be taken as evidence that Hürthle-cell tumors are not simply a subtype of follicular carcinoma.

There are no widely accepted criteria for the diagnosis of atypia or its absence in aspirates of thyroid nodules categorized as follicular or Hürthle-cell tumors. The criteria used in this study, as described in abbreviated form above, do not appear to differ greatly, nor do the figures showing aspirates of nodules with and without atypia in the paper. One can easily envision different cytopathologists disagreeing about the presence or absence of atypia in aspirates. Even if there were no disagreement, the predictive value of atypia is limited, and therefore its presence or absence should not be a basis for advising for or against surgery in patients with a follicular tumor or Hürthle-cell tumor.

Robert D. Utiger, M.D.

No clinical or pathologic findings predict the presence of carcinoma in the contralateral thyroid lobe in patients with papillary thyroid carcinoma

Grigsby PW, Reddy RM, Moley JF, Hall BL. Contralateral papillary thyroid cancer at completion thyroidectomy has no impact on recurrence or survival after radioiodine treatment. Surgery 2006;140:1043-9.

SUMMARY

Background Most patients with a thyroid nodule that is likely to be a papillary carcinoma are treated by near-total thyroidectomy, one reason being that the contralateral thyroid lobe may contain one or more foci of carcinoma. However, some patients are treated by thyroid lobectomy if the probability that the nodule is a carcinoma is low. If the nodule proves to be a papillary carcinoma, or there is another nodule that is a papillary carcinoma, completion thyroidectomy is advised. This report describes an analysis of 150 patients who underwent completion thyroidectomy to determine the frequency and the factors associated with papillary carcinoma in the contralateral lobe.

Methods The study subjects were 150 patients (114 women, 36 men; mean age, 42 years) who had undergone thyroid lobectomy for a nodule that proved to be a papillary carcinoma. They underwent completion thyroidectomy 3±8 (mean±SD) months later, and subsequently were treated with radioiodine. Seventy-five patients (50 percent) had a classical papillary carcinoma and 75 (50 percent) the follicular variant subtype of papillary carcinoma.

Results Sixty-two of the 150 patients (41 percent) had a papillary carcinoma in the contralateral lobe and 88 (59 percent) did not. There were no differences in the proportions of women and men, age, or interval between the initial thyroid lobectomy and the completion thyroidectomy in the two groups. Similarly, there were no statistically significant differences in the type of primary papillary carcinoma (classical vs. follicular variant) or the size of the primary tumor or the initial pathologic findings in the two groups (Table 1).

Table 1. Characteristics of the Primary Papillary Carcinoma in Patients Who Underwent Completion Thyroidectomy.

	Tumor in Contralateral Lobe (n=62)	No Tumor in Contralateral Lobe (n=88)
Size of primary tumor (cm)	2.1	2.5
Tumor in cervical lymph nodes	17 (27%)	19 (22%)
Tumor at margin of specimen	19 (31%)	17 (19%)
Soft-tissue invasion	15 (24%)	12 (14%)

There was no relationship between the size of the primary papillary carcinoma and the presence of contralateral papillary carcinoma (Table 2).

Table 2. Relationship between Size of Primary Papillary Carcinoma and Frequency of Contralateral Papillary Carcinoma.

Size of Primary Tumor	No. of Patients	No. with Contralateral Tumor
0.1 to 0.5 cm	9	3 (33%)
0.6 to 0.9 cm	16	8 (50%)
1.0 to 1.5 cm	31	17 (55%)
1.6 to 2.0 cm	28	12 (43%)
>2.0 cm	66	22 (33%)

During follow-up (up to 20 years, mean duration not stated), 4 of the 62 patients with contralateral carcinoma (6 percent) had a recurrence, as compared with 2 of the 88 patients with no contralateral carcinoma (2 percent) (difference not statistically significant).

Conclusion A substantial proportion of patients with papillary carcinoma have carcinoma in the contralateral thyroid lobe. There are no clinical or pathologic features that distinguish these patients from those who do not have carcinoma in the contralateral lobe, and the recurrence rates in the two groups are similar.

COMMENTARY

Multifocality, whether in the same or the contralateral lobe of the thyroid, is a feature of papillary carcinoma, and the 41 percent frequency of a focus of papillary carcinoma in the contralateral lobe in this study is within the range found in other studies. (Patients with follicular carcinoma may also have multiple tumors, but not as often.) In this study, the presence of papillary carcinoma in the contralateral lobe was not related to the type of carcinoma (classical vs. follicular variant), the size of the main carcinoma, or any operative or pathologic findings. What is not described is how many patients had one or more separate foci of carcinoma in the lobe with the main tumor, how many foci were present in the contralateral lobe, and the size and pathologic characteristics of these foci.

The latter findings are relevant to the question of whether multiple foci of papillary carcinoma are metastases of the main tumor or independent tumors. Data from molecular analyses on this point are contradictory. The findings are also relevant to the practical question of the need for completion thyroidectomy.

Completion thyroidectomy has gained acceptance because the contralateral lobe often contains one or more usually small foci of carcinoma, but multicentricity is not considered a determinant of prognosis of papillary carcinoma, and the likelihood of clinically important recurrence in the contralateral lobe if it is left in situ is very low. This suggests that small foci of cells that look like papillary-carcinoma cells may not behave like papillary carcinoma biologically. Rather than completion thyroidectomy, why not perform thyroid ultrasonography, if not already done, and no more surgery if there are no nodules in the remaining thyroid lobe, and then perform ultrasonography periodically thereafter? Alternatively, the remaining lobe could be destroyed with radioiodine; although small foci of carcinoma probably do not concentrate radioiodine, the radiation from the radioiodine concentrated by the surrounding normal tissue should destroy these foci.

Robert D. Utiger, M.D.

Undetectable basal serum thyroglobulin concentrations, measured using a sensitive assay, are strong evidence against recurrent thyroid carcinoma

Smallridge RC, Meek SE, Morgan MA, Gates GS, Fox TP, Grebe S, Fatourechi V. Monitoring thyroglobulin in a sensitive immunoassay has comparable sensitivity to recombinant human TSH-stimulated thyroglobulin in follow-up of thyroid cancer patients. J Clin Endocrinol Metab 2007;92:82-7.

SUMMARY

Background The presence of thyroglobulin in the serum of patients with thyroid carcinoma who have been treated indicates the presence of persistent or recurrent carcinoma. However, the sensitivity of many serum thyroglobulin assays is limited, and a rise in serum thyroglobulin after stimulation with endogenous or exogenous thyrotropin (TSH) has proven more sensitive than basal measurements as an indicator of the presence of persistent or recurrent thyroid carcinoma. In this study, the value of a more sensitive assay for serum thyroglobulin was evaluated to determine whether basal measurements could supplant the need for measurements after TSH stimulation.

Methods The main study subjects were 80 patients (59 women, 21 men; mean age, 53 years) with papillary carcinoma (64 patients) or follicular or Hürthle-cell carcinoma (16 patients) who had undetectable basal serum thyroglobulin concentrations and undetectable serum antithyroglobulin antibody concentrations. They had been treated by surgery and with radioiodine at an average age of 45 years, and none had evidence of recurrence at the time of the study. All were taking thyroxine (T_4), and with few exceptions their serum TSH concentrations were low.

After measurement of basal serum thyroglobulin, the patients were given two 0.9-mg intramuscular doses of recombinant TSH at a 24-hour interval, and serum thyroglobulin was measured again two or three days after the last injection. Most of the patients also underwent radioiodine (I-131) imaging after the TSH injections or ultrasonography of the neck. Serum thyroglobulin was measured using an immunoradiometric assay with a functional sensitivity of 0.1 ng/ml. The results of TSH stimulation testing in these 80 patients were compared with the results in 50 similar patients with basal serum thyroglobulin concentrations of 0.1 to 2.0 ng/ml.

Results Serum thyroglobulin concentrations after TSH administration were <0.1 ng/ml in 47 patients (59 percent), <2.0 ng/ml in 29 patients (36 percent), and 1.0 to 3.0 ng/ml in the remaining 4 patients (5 percent). In contrast, among 33 similar patients with basal serum thyroglobulin concentrations of 0.1 to 0.5 ng/ml, 8 (24 percent) had serum thyroglobulin concentrations >2.0 ng/ml after TSH stimulation, as did 14 of 17 patients (82 percent) with basal serum thyroglobulin concentrations of 0.6 to 2.0 ng/ml.

I-131 imaging, done in 77 patients with basal serum thyroglobulin concentrations <0.1 ng/ml, revealed no uptake in 70 (91 percent). Ultrasonography of the neck in 72 of these patients revealed no abnormalities suggestive of recurrent carcinoma. (The results of these tests in the 50 patients with serum thyroglobulin concentrations of 0.1 to 2.0 ng/ml are not given.)

Follow-up TSH-stimulation testing and imaging in the patients with basal serum thyroglobulin concentrations <0.1 ng/ml revealed little change in serum thyroglobulin responses or no other evidence of recurrent carcinoma, except for one patient who had recurrent carcinoma in a cervical lymph node 1 year after initial testing.

Conclusion Patients with thyroid carcinoma who have undetectable serum thyroglobulin concentrations, as measured using a very sensitive assay, while taking T_4 are at very low risk of recurrent carcinoma. Use of such a sensitive assay obviates the need for measurements of serum thyroglobulin after either exogenous or endogenous TSH stimulation.

COMMENTARY

Patients with thyroid carcinoma who have readily detectable basal serum thyroglobulin concentrations when their serum TSH concentrations are normal or low are presumed to have persistent or recurrent thyroid carcinoma. In them, measurement of serum thyroglobulin after cessation of T_4 therapy or exogenous administration of TSH has little value. Instead, the next step should be a search for site(s) of thyroglobulin production.

In patients who have undetectable or very low basal serum thyroglobulin concentrations, a substantial increase in response to endogenous or exogenous TSH stimulation is a sensitive but not specific indicator of persistent or recurrent thyroid carcinoma. These patients probably have some thyroglobulin in their serum at all times, but the amount is too small to be measured when their serum TSH concentrations are not high. If they did not, then it would be necessary to postulate that thyroglobulin was produced and secreted only when serum TSH concentrations were high, which seems unlikely. In short, the more sensitive the assay for serum thyroglobulin, the greater the likelihood that an undetectable value means there is no remaining thyroid tissue, normal or otherwise, therefore making it unnecessary to measure serum thyroglobulin after TSH stimulation.

Based on the results presented by Smallridge et al., a serum thyroglobulin assay with a sensitivity of 0.1 ng/ml is not quite sensitive enough to identify those patients who have absolutely no serum thyroglobulin, because 33 of their 80 patients (41 percent) with undetectable basal serum thyroglobulin concentrations had some increase in serum thyroglobulin in response to TSH stimulation. But the increases in these patients were very small, and none had other evidence of recurrent carcinoma. So it is reasonable to conclude that the presence of an undetectable basal serum thyroglobulin value in any patient is strong evidence against the presence of tumor. Hopefully, serum thyroglobulin assays with this, or greater, sensitivity will soon become widely available.

Robert D. Utiger, M.D.

Thyroid function changes little with time in many children with Hashimoto's thyroiditis

Radetti G, Gottardi E, Bona G, Corrias A, Salardi S, Loche S; Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED). The natural history of euthyroid Hashimoto's thyroiditis in children. J Pediatr 2006;149:827-32.

SUMMARY

Background Hashimoto's thyroiditis is the most common cause of thyroid disease in children, but relatively little is known about its natural history. This study was done to determine the course of Hashimoto's thyroiditis in a large group of children who were euthyroid or had subclinical hypothyroidism at the time of diagnosis.

Methods A total of 160 children (117 girls, 43 boys) with Hashimoto's thyroiditis followed at 20 pediatric endocrinology centers in Italy were studied retrospectively. The criteria for inclusion in the study were typical ultrasonographic abnormalities (not defined), high serum concentrations of antithyroid peroxidase (anti-TPO) antibodies or anti-thyroglobulin (anti-Tg) antibodies, and serum thyrotropin (TSH) concentrations <2 times the upper limit of normal. The disorder was discovered because the child had a goiter, incidentally during a check-up, or during evaluation of children with diabetes mellitus (74 children), celiac disease (17 children), Turner's syndrome (20 children), and Down's syndrome (3 children). Growth data were collected, thyroid ultrasonography was done, and serum TSH, free thyroxine (T_4), and anti-TPO and anti-Tg antibodies were measured at base line and during follow-up. Children with serum TSH concentrations >2 times the upper limit of normal at base line were treated with T_4 and excluded, as were those whose serum TSH concentrations increased to this level during follow-up.

Results At the time of diagnosis, 105 children (66 percent) (mean age, 10 years) had normal serum TSH concentrations and 55 (34 percent) (mean age, 9 years) had high concentrations (<2 times the upper limit of normal). The height and body mass index of the children in each group were normal for age and sex, and approximately 40 percent in each group had thyroid enlargement, 75 percent had high serum anti-TPO antibody concentrations, and 60 percent high serum anti-Tg antibody concentrations.

The median duration of follow-up was 5 years (range, 0.1 to 33). Among the 160 children, the final serum TSH concentration was normal in 84 (53 percent), <2 times the upper limit of normal in 26 (16 percent), and >2 times the upper limit of normal in 50 (31 percent). The concentration increased to >2 times the upper limit of normal in 27 children (26 percent) of those with normal initial values and 23 (42 percent) of those with initial values <2 times the upper limit of normal. The results were similar in the children with no associated disorders.

The initial clinical findings and serum TSH and anti-TPO antibody concentrations were similar in the children whose serum TSH concentrations did not increase or decreased and those whose serum TSH concentrations increased during follow-up, whereas the initial thyroid volume and serum anti-Tg antibody concentrations were higher in the latter group.

Statural growth was normal during follow-up in all the children, including those in whom serum TSH concentrations increased to >2 times the upper limit of normal.

Conclusion Among children with Hashimoto's thyroiditis who have normal or slightly high serum TSH concentrations at the time of diagnosis, the concentrations may increase, not change, or decrease with time.

COMMENTARY

The natural history of Hashimoto's thyroiditis in children is variable. Previous retrospective studies have described persistently normal thyroid function in some children, spontaneous resolution of hypothyroidism in others, and progression to subclinical hypothyroidism (meaning serum TSH values <2 times the upper limit of normal with respect to this study) or overt hypothyroidism (serum TSH >2 times the upper limit of normal) in still others. This study confirms these outcomes in a large cohort of children. The only base-line factors associated with progression were larger thyroid volume and higher serum anti-Tg antibody concentrations, but it is unlikely that there are any cut-off values for either that could be used to guide initiation of T_4 therapy.

Growth failure has been considered to be a sensitive indicator to the presence of hypothyroidism In this regard, the height of the children studied by Radetti et al. was normal at base line, and there were no differences in mean height standard deviation scores at base line or last follow-up between the children whose thyroid function deteriorated during follow-up as compared with the children whose thyroid function remained the same or normalized. Presumably, close follow-up of these children led to early recognition of overt hypothyroidism before their growth had slowed.

Children who have Hashimoto's thyroiditis and are euthyroid can be followed without T_4 therapy, because they may remain euthyroid indefinitely (few have been followed to adulthood). So, too, may children with subclinical hypothyroidism, because their thyroid function may improve spontaneously. However, overt hypothyroidism developed in a substantial minority of these 160 children (31 percent of all children and 42 percent of those with subclinical hypothyroidism in this study). Because there is no way to identify the children whose thyroid function will decline, biochemical surveillance with serial measurements of serum TSH is indicated for all children with Hashimoto's thyroiditis regardless of their functional status at presentation.

Stephen A. Huang, M.D.
Children's Hospital
Boston, MA

Radioiodine decreases thyroid size in patients with Hashimoto's thyroiditis

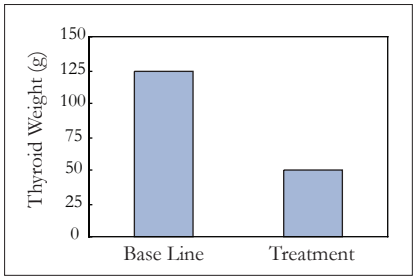
Tajiri J. Radioactive iodine therapy for goitrous Hashimoto's thyroiditis. J Clin Endocrinol Metab 2006;91:4497–500.

SUMMARY

Background Occasional patients with Hashimoto's thyroiditis have thyroid enlargement that is sufficient to cause compressive symptoms or cosmetic distress and that does not diminish in response to thyroxine (T_4) therapy. This report describes the effect of repeated doses of radioactive iodine (I-131) on thyroid size in such patients.

Methods The study subjects were 13 patients (11 women, 2 men; age range, 50 to 79 years) with Hashimoto's thyroiditis, as defined by the presence of goiter, hypothyroidism, thyroid ultrasonography, and high serum antithyroid antibody titers. The mean duration of thyroid enlargement was 12 years (range, 4 to 33 years). All the patients had been treated with T_4, with little change in thyroid size (duration of treatment not stated).

The T_4 therapy was stopped and the patients were asked to restrict their iodine intake for one month before and one week after each I-131 treatment, which ranged in number from two to six and was given at intervals of one to six months; they were followed at six-month intervals after the last treatment. Thyroid weight was measured at base line and periodically thereafter by ultrasonography. Thyroid I-131 uptake was measured 24 hours after the administration of 100 μCi (3.7 MBq) of I-131 before each treatment. The treatment doses were calculated from the formula: thyroid weight (g) × (120 μCi [4.4 MBq] ÷ 24-hr I-131 uptake [% of dose]) × 10. The calculated dose always exceeded the maximum allowable outpatient dose (13.5 mCi [500 MBq]), and therefore to avoid hospitalization the patients were treated with 13 mCi (481 MBq). The absorbed dose was then measured.



Results At base line, the patients' mean thyroid weight was 125 g (range, 43 to 269). The mean number of treatments was 5 (range, 2 to 6), and the mean total dose of I-131 was 60 mCi (2220 MBq) (range, 25 to 78 [925 to 2886]). The mean thyroid weight at last follow-up 26 to 66 months (mean, 48) after the first treatment was 50 g (range, 18 to 93), a 59 percent (range, 36 to 84) decrease from base line (Figure). The decrease was correlated with the total absorbed dose of radiation, and 9 of the 10 patients in whom the absorbed dose was >100 Gy had a >50 percent decrease in thyroid weight.

The mean 24-hour I-131 uptake values before the first and the last doses of I-131 were 36 percent (range, 7 to 66) and 21 percent (range, 7 to 48), respectively. Despite the fall in mean 24-hour I-131 uptake, there were considerable variations (both increases and decreases) in individual patients.

At base line, the mean serum TSH concentration after cessation of T_4 therapy was 6.4 mU/L (range, 0.15 to 30.3). The value at the time of the last dose of I-131 was 29.4 mU/L; only two patients did not have hypothyroidism at this time. Serum antithyroid antibody titers decreased in six patients and did not change or increased in the other seven patients.

Conclusion Repeated doses of radioiodine result in substantial reduction in thyroid size in patients with Hashimoto's thyroiditis who have a large goiter.

COMMENTARY

The causes of goiter in patients with Hashimoto's thyroiditis include thyroid follicular-cell hyperplasia, infiltration with lymphocytes and formation of lymphoid germinal centers, and fibrosis. The hyperplasia would be expected to be TSH-dependent, and therefore to decrease in response to treatment with T_4. Lymphocytic infiltration and even germinal-center formation might also decrease in response to T_4, if decreased TSH secretion resulted in decreased expression of thyroid antigens and therefore decreased activation of cell- and antibody-mediated thyroid autoimmunity. Fibrosis, on the other hand, would presumably be irreversible.

What happens in practice? In a six-month study of 23 patients with Hashimoto's thyroiditis, T_4 therapy resulted in variable decreases in thyroid size, and the decreases were greater in patients with overt hypothyroidism than in those with subclinical hypothyroidism (1). In a study of 43 patients followed for 10 to 20 years, most of whom were euthyroid at base line and many of whom were treated with thyroid hormone, thyroid size did not change in 49 percent, decreased in 46 percent, and increased in 5 percent (2). Thyroid biopsies at base line and at follow-up in 12 patients revealed little change.

The patients studied by Tajiri had also benefited little from chronic T_4 therapy. They did benefit from I-131 therapy, at the cost of more hypothyroidism. Whether so many doses were needed is not clear; the criteria used to determine whether and when to give more I-131 are not specified. For patients like these who need or want something done to reduce thyroid size substantially, I-131 therapy may be as attractive as surgery (although not as effective), especially if it can achieved with fewer doses, as might be possible by stimulation of thyroid I-131 uptake with exogenous TSH.

Robert D. Utiger, M.D.

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Targeted screening during early pregnancy does not identify many women with thyroid dysfunction

Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? J Clin Endocrinol Metab 2007;92:203-7.

SUMMARY

Background Subclinical hypothyroidism in pregnant women may be associated with adverse effects on the pregnancy and the fetus. This has led to the suggestion that all pregnant women or at least those at high risk for thyroid dysfunction should be screened by measurement of serum thyrotropin (TSH). This study was undertaken to determine the efficacy of screening pregnant women at increased risk of thyroid dysfunction, as compared with screening all pregnant women.

Methods Serum TSH and free thyroxine (T_4) were measured in 1560 consecutive pregnant women (mean age, 27 years) at the time of their first prenatal visit (median, 9 weeks; range, 6 to 22). Most 1426 (91 percent) were white, 62 (4 percent) were South Asian, and 72 (5 percent) were of other race/ethnicity. The women were subdivided into high- or low-risk groups based on the presence or absence of a personal or family history (in first- or second-degree relatives) of a thyroid disorder or therapy for a thyroid disorder or a personal history of a nonthyroidal autoimmune disorder. Their serum TSH values were compared with those of normal nonpregnant women and men (serum TSH, 0.27 to 4.2 mU/L).

Results Among the 1560 women, 1399 (90 percent) had a normal serum TSH concentration, 40 (3 percent) a high concentration, and 121 (7 percent) a low concentration (Table 1). The frequency of high concentrations was higher in the high-risk than in the low-risk women (7 vs. 1 percent), whereas the frequency of low concentrations was similar in these two groups (9 vs. 7 percent). Among the 40 women with high serum TSH concentrations, 8 (20 percent) had values >10 mU/L and 16 (40 percent) had low serum free T_4 concentrations.

Table 1. Serum TSH Concentrations in 1560 Women Who Were 6 to 22 Weeks Pregnant.

	No.	Normal	High	Low
All women	1560	1399 (90%)	40 (3%)	121 (7%)
Low-risk women	1147	1051 (92%)	12 (1%)	84 (7%)
High-risk women	413	348 (84)	28 (7%)	37 (9%)

The results in the high-risk women according to the individual risk factors are shown in Table 2. All these factors were associated with a significant increase in the likelihood of a high serum TSH concentration, but not a low concentration. Serum TSH concentrations were not related to age, smoking history, parity, or history of miscarriage.

Table 2. Serum TSH Concentrations in 413 High-Risk Women According to Risk Factor.

Risk Factor	No.*	Normal	High	Low
Known thyroid disorder	89	59 (66%)	17 (19%)	13 (15%)
Taking T_4	35	19 (54%)	8 (23%)	8 (23%)
Nonthyroidal autoimmune disorder	17	14 (82%)	2 (12%)	1 (6%)
Thyroid disorder in family	356	305 (86%)	20 (56%)	31 (9%)

*Some women had more than 1 risk factor.

The first-trimester reference range based on posthoc analysis of the results in the women in the low-risk group was 0.09 to 3.03 mU/L. Based on this range, 98 women (6 percent) had high serum TSH concentrations, of whom 54 were in the high-risk group and 44 in the low-risk group.

Conclusion A substantial proportion of women with abnormal serum TSH concentrations during early pregnancy do not have risk factors for thyroid dysfunction, and therefore will be missed if only pregnant women with these risk factors are screened for thyroid dysfunction.

COMMENTARY

The goal of testing pregnant women for thyroid dysfunction is to identify those with hypothyroidism, in particular subclinical hypothyroidism. It is the most common abnormality in these women, in whom it is associated with increased rates of miscarriage and preterm delivery, and possibly neurodevelopmental abnormalities in their children. The frequency of the first two abnormalities may be reduced by treatment with T_4, but whether the frequency of the latter is reduced is not known.

Apart from the uncertainty of the benefits of T_4 therapy in these women, there are both practical and substantive objections to screening. There is the need for gestational age-specific reference ranges for serum TSH. The optimal time for screening is not known. Intuitively, it would seem that earlier is better, but the time of peak frequency of hypothyroidism during pregnancy is not known. Hypothyroidism, whenever found, may not persist; serum TSH has rarely been measured more than once. Then there is the question of whether the screening test should be measurement of serum TSH or of free T_4, given that T_4 deficiency, not TSH excess, is most likely responsible for any adverse outcomes.

Finally, little is known about the causes of hypothyroidism in pregnant women. The most common cause may be chronic autoimmune thyroiditis. But it could be iodine deficiency. In 2001–2002, the frequency of mild iodine deficiency (urinary iodine excretion <100 μg/L) among pregnant women in the United States was 38 percent, and the frequency of moderate iodine deficiency (urinary iodine excretion <50 μg/L) was 7 percent (1). Increasing iodine intake in pregnant women in women with subclinical hypothyroidism and marginal iodine intake not only lowers serum TSH concentrations but also improves the outcome of pregnancy (2). Given these results and the uncertainties of screening, increasing iodine intake in pregnant women seems more sensible than screening.

Robert D. Utiger, M.D.

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The retinoid receptor agonist bexarotene inhibits thyrotropin secretion in normal subjects

Golden WM, Weber KB, Hernandez TL, Sherman SI, Woodmansee WW, Haugen BR. Single-dose rexinoid rapidly and specifically suppresses serum thyrotropin in normal subjects. J Clin Endocrinol Metab 2007;92:124-30.

SUMMARY

Background Bexarotene is a retinoid (rexinoid) that is approved for treatment of patients with cutaneous T-cell lymphoma. It has caused central hypothyroidism in patients treated for several weeks or longer. This study was done to determine the acute effects of a single dose of bexarotene in normal subjects.

Methods The study group consisted of 6 normal subjects (5 women, 1 man; age range, 24 to 53 years). Their base-line serum thyrotropin (TSH) concentrations ranged from 0.7 to 3.0 mU/L and their free thyroxine (T_4) concentrations from 0.6 to 1.0 ng/dl (7.7 to 12.9 pmol/L). They were given, in random order, bexarotene in a dose of 400 mg/m^2 or placebo by mouth in the morning after an overnight fast. Blood samples for measurements of serum TSH, free T_4, total T_4, total triiodothyronine (T_3), T_3-resin uptake, and cortisol were obtained at base line and at frequent intervals for 48 hours after administration of bexarotene or placebo. Serum prolactin was measured at base line and 24 hours. Serum free T_4 index and free T_3 index values were calculated as the product of the serum total T_4 or total T_3 and the T_3-resin uptake. The subjects were not fed for four hours after drug or placebo administration.

Results The mean (±SE) serum TSH concentration decreased progressively from 1.43±0.08 mU/ml at base line to a nadir of 0.32±0.02 mU/L 24 hours after bexarotene administration (a decrease of 78 percent), after which it increased slightly (Table). There was a transient decrease in serum TSH concentrations from 1.47±0.11 mU/L to approximately 0.8 mU/L in the first 8 hours after administration of placebo, after which the values were similar to the base-line value.

Table. Mean Serum TSH Concentrations after Administration of Bexarotene or Placebo in Six Normal Subjects.*

Serum TSH (mU/L)	Bexarotene	Placebo
Base line	1.4	1.5
4 hours	0.7	0.9
8 hours	0.6	0.8
12 hours	0.5**	1.2
24 hours	0.3**	1.5
48 hours	0.5**	1.7

Most values extrapolated from Figure 1 of the paper.
**P <0.05, as compared with placebo.

As compared with placebo, the mean serum free T_4 index value, but not free T_4 concentration, was significantly lower 48 hours and the mean serum free T_3 index values were significantly lower 12, 24, and 48 hours after bexarotene administration. There were no differences in serum cortisol or prolactin concentrations (the former varied appropriately according to the time of day) after bexarotene and placebo administration.

Conclusion Single doses of the retinoid bexarotene inhibit TSH secretion substantially for 48 hours.

COMMENTARY

It is clear from this study that bexarotene acutely inhibits TSH secretion, leading to a small fall in serum free T_4 index and free T_3 index values, and presumably serum free T_4 and free T_3 concentrations. The inhibition of TSH secretion cannot be attributed to an increase in serum cortisol, which is known to inhibit TSH secretion transiently. Nor was there a fall in prolactin secretion, which can fall, as does TSH secretion, if there is a fall in thyrotropin-releasing hormone secretion.

Sustained administration of bexarotene in similar or higher doses in patients with cutaneous T-cell lymphoma clearly causes central hypothyroidism (1). Among 27 patients treated with doses in the range of 300 mg/m^2 daily, the mean serum TSH concentration decreased from 2.2 mU/L to a nadir of 0.05 mU/L and serum free T_4 and T_3 concentrations decreased by 55 and 38 percent, respectively. Many of the patients had symptoms of hypothyroidism, notably easy fatigability and cold intolerance, which improved when they were treated with T_4. Their pituitary–thyroid function was normal after cessation of bexarotene (and T_4, if given).

Bexarotene is thought to inhibit TSH secretion directly. It binds to retinoid X receptors, and the bexarotene-receptor complexes inhibit transcription of the gene for the β-subunit of TSH. It therefore mimics the action of T_3, because T_3 bound to its receptors has a similar inhibitory effect on TSH synthesis. In most other tissues, the receptor-mediated actions of T_3 are stimulatory. The effect of chronic bexarotene administration to cause symptoms of hypothyroidism indicates that the bexarotene-receptor complexes do not activate the genes that are activated by T_3-receptor complexes. Instead, the effects of the fall in serum T_4 and T_3 concentrations are manifest.

A drug that inhibits TSH secretion without having thyromimetic actions in other tissues has long been sought. The most obvious use for such a drug would be to inhibit TSH secretion in patients with thyroid carcinoma and other thyroid disorders in which inhibition of TSH secretion might be beneficial, for example, in patients with a TSH-secreting pituitary adenoma. Some might add to this list euthyroid patients with a thyroid nodule or multinodular goiter, but the evidence that decreasing TSH secretion is beneficial in these patients is sparse. Bexarotene is probably not that long-sought drug (it has many side effects), but it could point the way.

Robert D. Utiger, M.D.

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Increasing thyroid dysfunction is correlated with degree of illness and mortality in intensive-care-unit patients

Plikat K, Langgartner J, Buettner R, Bollheimer LC, Woenckhaus U, Scholmerich J, Wrede CE. Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. Metabolism 2007;56:239-44.

SUMMARY

Background There are changes in serum thyroid hormone and thyrotropin (TSH) concentrations in patients with all nonthyroidal illnesses, and the frequency and severity of the changes increase in proportion to the severity of the illnesses. In this study, pituitary–thyroid function was assessed in patients admitted to an intensive–care unit (ICU), and the results correlated with severity of illness and other outcomes.

Methods Serum free triiodothyronine (T_3), free thyroxine (T_4), and TSH were measured in 247 patients soon (median time, 1 day) after admission to an ICU. There were 125 women and 122 men; their mean age was 59 years. The mean stay in the unit was 10 days, during which 122 (49 percent) required mechanical ventilation and 45 (18 percent) died. Among them, 27 patients who were taking an antithyroid drug or T_4 were excluded from further analysis.

During the same period another 496 patients were admitted to the same unit, but did not have these three tests. Their stay was shorter (mean, 4 days), fewer required mechanical ventilation (36 percent), and 17 percent died.

For the 220 patients who had all three thyroid tests, the Acute Physiology and Chronic Health Examination II (APACHE II) score was calculated within 24 hours after admission and main diagnoses were recorded.

Results Seventy-nine of the 220 patients (36 percent) were euthyroid, as defined by normal serum free T_3, free T_4, and TSH concentrations, and 97 (44 percent) had low serum free T_3 concentrations. Among the latter, 52 (24 percent) had normal serum TSH concentrations, 45 (20 percent) had low serum TSH concentrations, and 24 (11 percent) had low serum free T_4 concentrations. Twenty-nine patients (13 percent) had only low serum TSH concentrations. Six patients (3 percent) had low serum free T_3, free T_4, and TSH concentrations, and 1 (0.4 percent) had high serum free T_3 and free T_4 concentrations.

The APACHE II score, duration of stay in the ICU, and need for mechanical ventilation were lowest in the patients with normal serum free T_3 and free T_4 concentrations and highest in the patients with low serum free T_3 and free T_4 concentrations (Table). The results in the latter two groups were similar in the patients who had low serum TSH concentrations and those who had normal concentrations.

Table. Mean APACHE II Score, Length of ICU Stay, and Need for Mechanical Ventilation in Relation to Serum Free T_3, Free T_4, and TSH Concentrations Soon after Admission in 220 ICU Patients.

	No.	APACHE II Score	ICU Stay (days)	Mechanical Ventilation (n)
Normal	79	12.5	3	35 (44%)
Low serum free T_3	97	18*	5*	48 (50%)*
Low serum free T_3 and free T_4	24	21*	13*	20 (83%)*

*P<0.05, as compared with the normal group.

The ICU mortality rate in the patients with normal serum free T_3 and free T_4 concentrations was 13 percent, and it was 18 percent in the patients with low serum free T_3 concentrations (P=0.40) and 46 percent in the patients with low serum free T_3 and free T_4 concentrations (P<0.01). The frequency of low serum free T_3 concentrations was not related to diagnosis.

Conclusion Among patients admitted to an ICU, illness severity, length of stay, and mortality were higher in those with low serum free T_3 and free T_4 concentrations than in those with low or normal serum free T_3 concentrations.

COMMENTARY

This study confirms that thyroid dysfunction is very common in patients with nonthyroidal illness and that severity of illness and mortality in these patients are correlated with the changes. The study obviously was retrospective, and the tests must have been done, or not done, according to the dictates of multiple physicians. It is unlikely that the results would have been much different if all admitted patients had been studied, or if the measurements had been done later after admission.

Serum free T_3 and free T_4 were measured by chemiluminescent immunoassays. The results of these measurements in patients with nonthyroidal illness may vary according to the immunoassay used (1), but this is nearly always a matter of degree and the results are not much different when the measurements are done by equilibrium dialysis or ultrafiltration. These variations are probably mostly due to quantitative or qualitative changes in one or more of the serum thyroid hormone–binding proteins or the presence in serum of various substances not present in normal subjects that affect the in vitro measurements.

These variations do not alter the fact that some patients with nonthyroidal illnesses have illness-related central hypothyroidism, with normal or low serum TSH concentrations. The hypothyroidism is more the result of excessive T_3 and T_4 clearance than decreased thyroidal secretion, because serum T_3 and T_4 concentrations fall during nonthyroidal illness even in patients with hypothyroidism who are taking T_4 (2). What remains unknown—more than 30 years after the phenomenon was recognized—is whether the changes are beneficial or harmful.

Robert D. Utiger, M.D.

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

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