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Clinical Thyroidology

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Finding Material for *Clinical Thyroidology*

Clinical Thyroidology is a derivative journal, because its content is derived from original research published elsewhere. How comprehensive is the search for this original research, and what criteria are used to select articles for abstracting and commentary?

To identify candidate articles, I use a service that searches approximately 2500 biomedical journals, looking for titles and abstracts that contain one or more of about 50 words or terms relevant to thyroid physiology and disease, including eponyms. A search is done each week and the titles and abstracts of the articles are sent to me by Email to review.

The goal is not to miss anything, and that seems unlikely given that each week's list contains 60 to 80 articles. Among these articles, some are really about other subjects, and the thyroid is mentioned only in passing. Others are thyroid-related, but too far distant from clinical thyroidology to be suitable for *Clinical Thyroidology*. Still others are editorials, letters to the editor, or reviews. These types of articles are already derivative material, although some of the review articles are listed inside the back cover.

The approximately 10 to 15 articles that remain need to be looked at in their entirety in a library or on the Internet if the full text is available. Often, abstracts are incomplete, even misleading, and the conclusions are overly enthusiastic. Fortunately, I have access to an excellent medical library, the Countway Library of the Harvard Medical School, and if an article is in a journal that is not among the library's holdings it can be obtained in a few weeks by interlibrary loan.

The questions that I ask when I look at articles for abstracting and commentary include the following. Was the study original? If not, does it confirm or rebut an earlier study? Was it well done? Is the study important? Will it change practice? Does it open new areas for study? Is it interesting? Is it clear from the article what was done and what was found? (There is nothing like trying to abstract an article to make one see the article's deficiencies.) Is the study, or at least the topic of the study, worth commenting on? Has the topic been covered recently in the journal? Is the article in a journal not likely to be read by endocrinologists? Will selection of a particular article mean that too much space in an issue is devoted to a particular topic? The answers to most if not all these questions are subjective. I have no system for either ranking these questions or scoring the answers, and doubt that a useful system for either purpose could be devised.

So I choose whether well or not is for readers to decide. Let me know.

Robert D. Utiger, M.D.

ATA News & Upcoming Events

73rd Annual Meeting

The annual meeting of the ATA will be held at the Omni Shoreham Hotel in Washington, DC, from September 12 to 16, 2001. Preregistration material for the meeting was mailed in May and is available from the ATA office.

U.S. Nuclear Regulatory Commission Policy Regarding Use of Potassium Iodide in Case of a Nuclear Reactor Accident

The Nuclear Regulatory Commission (NRC) announced in December 2000 that it would require states to consider use of potassium iodide in planning for the emergency response to a nuclear reactor accident. The commission will provide funds to states that decide to acquire stores of potassium iodide to be used for this purpose. This decision was

based in large part on the efficacy of potassium iodide in reducing thyroidal uptake of radioactive iodine in several countries after the Chernobyl nuclear reactor accident in 1986.

Relevant documents are:

NRC news release: <http://www.nrc.gov/OPS/gmo/nrarcv/00-186.html>

FDA draft Guidance: Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies : <http://www.fda.gov/cder/guidance/3698dft.htm>

ATA release: http://www.thyroid.org/annonc/nrc_0101.htm

Verger P, Aurengo A, Geoffroy B, Le Guen B. Iodine kinetics and effectiveness of stable iodine prophylaxis after intake of radioactive iodine: a review. *Thyroid* 2001;11:353-60.

Opposite changes in plasma homocysteine concentrations in patients with hypothyroidism and hyperthyroidism

Diekman MJM, van der Put NM, Blom HJ, Tijssen JGP, Wiersinga WM. Determinants of changes in plasma homocysteine in hyperthyroidism and hypothyroidism. *Clin Endocrinol* 2001;54:197-204.

SUMMARY

Background High plasma homocysteine concentrations are associated with both arteriosclerotic vascular and venous thromboembolic disease. One cause of hyperhomocysteinemia is hypothyroidism; other causes include folic acid and vitamin B₁₂ deficiency, renal insufficiency, and genetic reductions in the activity of methylene-tetrahydrofolate reductase, the enzyme that catalyzes the methylation of homocysteine to form methionine. The role of these factors as determinants of plasma homocysteine concentrations was evaluated in this study done in the Netherlands.

Methods Plasma homocysteine, folate, vitamin B₁₂, and creatinine were measured in 50 consecutive patients with primary hypothyroidism and 46 consecutive patients with hyperthyroidism before treatment and again after they had been euthyroid for three months. In addition the patients were genotyped for a common genetic variant of methylene-tetrahydrofolate reductase (C677T), in which valine is substituted for alanine, that results in reduced enzyme activity and therefore reduced conversion of homocysteine to methionine. Among the patients with hypothyroidism, there were 37 women and 13 men; mean age, 45 years (range, 23 to 79). Among the patients with hyperthyroidism, there were 38 women and 8 men; mean age, 38 years (range, 22 to 77).

Results The mean plasma homocysteine concentration was higher before than after treatment in the patients with hypothyroidism and lower before than after treatment in the patients with hyperthyroidism (table), whereas there were

no changes in plasma folic acid or vitamin B₁₂ concentrations.

Table. Plasma Thyrotropin (TSH), Free Thyroxine, Homocysteine, Folic Acid, Vitamin B₁₂ and Creatinine Concentrations in Patients with Hypothyroidism or Hyperthyroidism before and after Treatment for 3 Months.

	Hypothyroid	Euthyroid	Hyperthyroid	Euthyroid
Plasma free thyroxine (ng/dL)	0.4±0.3	1.3±0.3	3.8±1.2	1.2±0.4
Plasma homocysteine (μmol/L)	17.6±10.2	13.0±4.7*	10.7±2.5	13.4±3.3*
Plasma folate (ng/mL)	5.2±2.8	5.9±2.5	6.7±3.4	6.0±2.9
Plasma vitamin B ₁₂ (pg/mL)	453±253	410±161	462±188	472±198
Plasma creatinine (mg/dL)	0.9±0.2	0.8±0.2*	0.6±0.2	0.8±0.2*

Conversion factors; plasma thyroxine x 12.87 = pmol/L; plasma folate x 2.27 = nmol/L; plasma vitamin B₁₂ x 0.738 = pmol/L; and plasma creatinine x 88.4 = μmol/L.

*P<0.005, as compared with before treatment.

There was a significant negative correlation between pre-treatment plasma homocysteine concentrations and plasma free thyroxine concentrations, independent of the other variables in the table. The frequency of the C677T allele of methylene-tetrahydrofolate reductase in the 96 patients (29 percent) was similar to that in the Dutch population.

Conclusion Thyroid status is a determinant of plasma homocysteine concentrations.

COMMENTARY

This detailed study provides some new information about the relationships between thyroid dysfunction, plasma homocysteine concentrations and other determinants of plasma homocysteine concentrations and the effects of thyroxine or antithyroid treatment on the concentrations and the effects of thyroxine. While much of the variation in plasma homocysteine concentrations could be attributed statistically to changes in plasma free thyroxine concentrations, the changes in plasma folate and creatinine concentrations probably contributed to the variation. In other studies patients with hypothyroidism and

hyperhomocysteinemia had slightly low plasma or red-cell concentrations of folate, perhaps the most important determinant of plasma homocysteine concentrations. However, the effect of folic acid supplements alone on plasma homocysteine concentrations in patients with hypothyroidism has not been studied.

It is noteworthy that plasma homocysteine concentrations rise soon after the onset of hypothyroidism. In several studies the concentrations were as high in hypothyroid patients 4 to 6 weeks after cessation of thyroxine therapy as in patients with chronic hypothyroidism (1,2).

References

1. Hussein WI, Green R, Jacobsen DW, et al. Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism. *Ann Intern Med* 1999;131:348-51.
2. Lien EA, Nedrebo BG, Varhaug JE, et al. Plasma total homocysteine levels during short-term iatrogenic hypothyroidism. *J Clin Endocrinol Metab* 2000; 85:1049-53.

Robert D. Utiger, M.D.

Low serum thyrotropin concentrations are a risk factor for hip fracture

Bauer DC, Ettinger B, Nevitt MC, Stone KL, for the Study of Osteoporotic Fractures Research Group. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Ann Intern Med* 2001;134:561-8.

SUMMARY

Background Patients with overt hyperthyroidism have biochemical evidence of decreased bone formation and increased bone resorption, and they may have osteopenia or even osteoporosis. The same changes can occur, although less often, in patients with subclinical hyperthyroidism. The extent to which patients in either group have an increased risk of fracture is not known.

Methods Between 1986 and 1988, 9704 white women aged >65 years were enrolled in a prospective study of risk factors for fracture. At baseline, the women were examined, serum samples were stored, and spine radiographs and measurements of the bone mass of the calcaneus by single-photon absorptiometry were done. Approximately 80 percent of the women had measurements of proximal femoral bone density 2 years later and spine radiographs 3.7 years later. They were asked about fractures every four months, and reported nontraumatic fractures were confirmed by review of the relevant radiographs. For the analysis of the relation between serum thyrotropin (TSH) values at baseline and fracture, serum TSH was measured in 148 of the 332 women (44 percent) who had hip fractures, 149 of the 389 women (38 percent) who had vertebral fractures, 100 of the 2520 women (4 percent) who had nonspine fractures and approximately twice as many women who had no fracture; the women in each fracture group and the respective control groups were randomly selected. The normal range for the serum TSH assay was 0.5 to 5.0 mU/L. Serum thyroxine was not measured.

Results At baseline, the women in each of the three fracture groups were slightly older than the women in the respective control group, they were slightly more likely to have a history of hyperthyroidism and be taking thyroid

hormone, and they had lower calcaneal and femoral neck bone density. The mean serum TSH concentrations were similar in all groups, as was the proportion of women who had serum TSH concentrations >5.5 mU/L; in contrast, the proportion of women in the three fracture groups who had serum TSH concentrations ≤0.1 mU/L was higher than in the respective control group (hip fracture group, 9.5 percent versus 2.6 percent; vertebral fracture group 9.4 percent versus 3.4 percent; nonspine fracture group, 6.0 percent versus 2.6 percent). Among the women with serum TSH concentrations ≤0.1 mU/L, 86 percent were taking thyroid hormone.

The women with serum TSH concentrations ≤0.1 mU/L at baseline had a greater than three times increased risk of hip or vertebral fracture, but not of nonspine fracture, during follow-up (table).

Table. Serum TSH Concentrations and the Risk of Fracture in Women.*

	Hip Fracture Relative Hazard Ratio**	Vertebral Fracture Relative Hazard Ratio	Nonspine Fracture Relative Hazard Ratio
Serum TSH normal	1.0 (reference)	1.0 (reference)	1.0 (reference)
Serum TSH >0.1 to <0.5 mU/L	1.9 (0.7-4.8)	2.8 (1.0-8.5)	2.0 (0.9-4.5)
Serum TSH ≤0.1 mU/L	3.6 (1.0-12.9)	4.5 (1.3-15.6)	2.3 (0.8-6.8)
Current thyroid hormone therapy	0.5 (0.2-1.3)	0.4 (0.2-1.3)	0.7 (0.3-1.7)
History of hyperthyroidism	2.2 (1.0-4.4)	1.3 (0.6-2.9)	0.9 (0.4-2.0)

*Adjusted for other variables on table and age, self-rated health, and estrogen therapy.
**95 percent confidence interval.

Conclusion Elderly white women with low serum TSH concentrations have an increased risk of hip and vertebral fracture.

COMMENTARY

This study was based on a large cohort of unselected women followed for several years and in whom the number of fractures was substantial, but the study has limitations. Why, for example wasn't serum TSH measured in all the women who had fractures, rather than a subset of them? We are told the intent was to avoid expensive biochemical measurements, but the cost of measurements of serum TSH in all the women who had hip or vertebral fractures and a few hundred more control women, with the resulting increase in statistical power and therefore firmer

conclusions, seems small given the overall costs of a study such as this. This seems even more important when viewed against an earlier study in this cohort of women in which low serum TSH concentrations were not associated with evidence of accelerated bone loss (1).

Serum thyroxine wasn't measured in any of the women, so we don't know how many had overt hyperthyroidism and how many had subclinical hyperthyroidism. However, 86 percent of the women with serum TSH concentrations ≤0.1 mU/L were taking thyroid hormone, and therefore were probably under some supervision, so it is likely

that many had subclinical hyperthyroidism rather than overt hyperthyroidism. Whether overt or subclinical most of the hyperthyroidism was preventable by reduction of the dose of thyroid hormone therapy.

Robert D. Utiger, M.D.

Reference

1. Bauer DC, Nevitt MC, Ettinger B, et al. Low thyrotropin levels are not associated with bone loss in older women: a prospective study. *J Clin Endocrinol Metab* 1997;82:2931-6.

Subclinical hyperthyroidism is associated with dementia in older people

Kalmijn S, Mehta KM, Pols HAP, Hofman A, Drexhage HA, Breteler MMB. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam Study. *Clin Endocrinol* 2000;53:733-7.

SUMMARY

Background Patients with subclinical hyperthyroidism by definition have normal serum thyroid hormone concentrations, and they usually have no or few symptoms of hyperthyroidism. The long-term risks of the disorder, although not precisely defined, may include overt hyperthyroidism, cardiac arrhythmias and dysfunction, and osteoporosis. Whether subclinical hyperthyroidism might be a risk factor for dementia was evaluated in a population-based study of healthy subjects aged 55 years and older in the Netherlands.

Methods The study cohort consisted of 1843 subjects (1141 women and 702 men) who did not have dementia and in whom serum thyrotropin (TSH) was measured at baseline. The subjects were screened for dementia using multiple tests (Mini-Mental State Examination, Geriatric Mental State schedule, Cambridge examination for disorders of the elderly, interviews, and brain imaging) at baseline and 2 to 4 years later (mean, 2.1 years). The diagnosis of dementia and of Alzheimer's disease was based on standard criteria (DSM-III-R and NIH, respectively).

Results Among the 1843 subjects, 25 (1.4 percent) developed dementia during the follow-up period; 19 of whom were considered to have Alzheimer's disease. The mean baseline serum TSH concentration in the dementia group was slightly lower than that in the no-dementia group, and the proportion of subjects with low values was statistically significantly higher ($P < 0.01$) (table).

	Dementia n=25	No Dementia n=1818
Age (mean [±SD] years)	78±5	69±7
Women	17 (68%)	1124 (62%)
Serum TSH (mean [±SD] mU/L)	1.4±1.1	2.2±3.5
Serum TSH <0.4 mU/L	5 (20%)	97 (5%)
Serum TSH >4.0 mU/L	1 (4%)	169 (9%)

Among the 102 subjects with baseline serum TSH concentrations <0.4 mU/L, the mean baseline serum thyroxine concentration was higher in those who became demented than in those who did not (9.5 µg/dL [122 nmol/L] versus 7.9 µg/dL [102 nmol/L]). At the time of the follow-up examination, the serum TSH concentration was still low in 75 percent of the subjects with initially low values who became demented, as compared with 51 percent of those who had not become demented.

The relative risk of dementia in the subjects with baseline serum TSH concentrations <0.4 mU/L, as compared with the subjects with normal baseline serum TSH concentrations, was 3.5 (95 percent confidence interval, 1.2 to 10.0). Considering the baseline serum TSH concentrations as a continuous variable in the group as a whole, the risk of dementia increased by 70 percent for each decrease in serum TSH concentration of one standard deviation (3.5 mU/L).

Conclusion Older subjects with subclinical hyperthyroidism are at increased risk of dementia.

COMMENTARY

The 1843 subjects in this study were randomly selected from a cohort of approximately 8000 subjects, and those treated for any type of thyroid disorder were excluded. The low serum TSH concentrations can be attributed to subclinical hyperthyroidism, rather than central hypothyroidism, given the serum thyroxine values cited above. Mental status was rigorously assessed, although the test scores are not provided, so we do not know how much the scores changed in either group during the follow-up

period. The most important limitations of the study, however, are that only 25 subjects developed dementia, and only 5 of them had low serum TSH concentrations at baseline. It would have been better if another round of mental status examinations and serum TSH determinations had been done 2 to 4 years later.

In epidemiological studies, thyroid disease, nearly always meaning overt thyroid disease, has not been identified as an important risk factor for dementia (1). Given the impairment in cognitive function that can occur in hypothyroidism, it would seem that subclinical hypothyroidism might be more of a risk

factor for dementia than subclinical hyperthyroidism. Stronger evidence that the latter is a risk factor for dementia is needed before such subjects are given antithyroid treatment in the hope of preventing it.

Robert D. Utiger, M.D.

Reference

1. Kokmen E, Beard CM, O'Brien PC, et al. Epidemiology of dementia in Rochester, Minnesota. *Mayo Clin Proc* 1996;71:275-82.

Administration of thyroxine during and after antithyroid drug therapy does not increase the frequency of remission of hyperthyroidism caused by Graves disease

Glinoeur D, de Nayer P, Bex M, and the Belgian Collaborative Study Group on Graves disease. Effects of L-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study. *Eur J Endocrinol* 2001;144:475-83.

SUMMARY

Background Administration of thyroxine (T_4) during and after antithyroid drug therapy in patients with Graves hyperthyroidism reduced the frequency of recurrent hyperthyroidism in a 1991 study, but not in several subsequent studies. This study was undertaken to readdress the role of T_4 therapy and also to look for other factors that might affect the frequency of recurrent hyperthyroidism in the patients with Graves hyperthyroidism,

Methods The study subjects were 82 patients (70 women and 12 men; mean age 36 years; range, 20 to 54) with untreated hyperthyroidism caused by Graves disease. At baseline, 11 were regular cigarette smokers, 63 had goiter and 25 had mild or moderate ophthalmopathy. All had overt biochemical hyperthyroidism, and 68 had high serum concentrations of thyrotropin (TSH)-receptor antibodies, as measured by radioreceptor assay.

The patients were treated with an antithyroid drug, nearly always (78 patients) methimazole (MMI), for 15 months. When they were euthyroid T_4 was added and subsequently adjusted to maintain serum TSH concentrations at <2.5 mU/L. At 15 months, MMI was discontinued and the patients were randomly assigned to receive 100 μ g of T_4 or placebo daily for 12 months. The patients were followed at 2-month intervals for the first 15 months and at 3-month intervals for the next 12 months. Recurrent hyperthyroidism was defined as clinical and overt biochemical hyperthyroidism that persisted after withdrawal of T_4 or placebo and remission as clinical and biochemical euthyroidism throughout the 12-month treatment period.

Results During the period of combined therapy, serum free T_4 and triiodothyronine (T_3) concentrations fell to normal in 1 to 2 months and remained normal thereafter. Serum TSH concentrations, initially undetectable, were normal in most patients in 2 to 6 months, and the median values ranged from 0.6 to 1.5 mU/L from 6 to 15 months. The mean T_4 dose increased from 85 μ g/day at 4 months to 115 μ g/day at 15 months.

The baseline characteristics of the patients assigned to T_4 or placebo were similar, as was the duration of MMI therapy. There were no differences in outcome during the 12-month period. Among the 40 patients in the placebo group, 28 (70 percent) remained euthyroid, 11 (28 percent) had recurrent hyperthyroidism, and 1 (2 percent) had transient hyperthyroxinemia. Among the 42 patients in the T_4 group, 23 (55 percent) remained euthyroid, 12 (28 percent) had recurrent hyperthyroidism, and 7 (17 percent) had transient hyperthyroxinemia.

Baseline variables not related to outcome were age, thyroid volume, presence of ophthalmopathy, and serum free T_4 , free T_3 and anti-TSH receptor antibody concentrations. Among the 11 smokers, 64 percent had a recurrence, as compared with 25 percent of the non-smokers. Among the 23 patients who had recurrent hyperthyroidism, 9 (39 percent) had high serum anti-TSH receptor antibody concentrations at the end of combined treatment, as compared with 1 (2 percent) of the patients who remained euthyroid.

Conclusion Among patients with Graves hyperthyroidism, administration of T_4 after a period of combined antithyroid drug and T_4 therapy was not associated with a decrease in the frequency of recurrent hyperthyroidism.

COMMENTARY

This is the latest in a series of studies that failed to confirm the 1991 study of Hashizume et al. (1), in which administration of MMI for 6 months, T_4 with MMI for 1 year, and then T_4 alone for 3 years was associated with a remarkably low rate (2 percent) of recurrent hyperthyroidism. Like the other negative studies, the design differed from that of Hashizume et al. These differences include not only patient variables, but also dose and duration of antithyroid

drug therapy and dose and duration of T_4 therapy. These variables might affect the likelihood of persistent or recurrent hyperthyroidism, or more fundamentally the likelihood of persistent Graves disease or remission of the disease, in many ways. These include the duration and degree of inhibition of thyroid secretion; the duration and degree of inhibition of TSH secretion; and effects on the function of T and B lymphocytes within the thyroid gland, whether secondary to changes in the structure of thyroid follicular cells, changes in

intrathyroidal T_4 and T_3 concentrations, or a direct action of the antithyroid drug on the lymphocytes.

Robert D. Utiger, M.D.

Reference

1. Hashizume K, Ichikawa K, Sakurai A, et al. Administration of thyroxine in treated Graves disease. Effects on the levels of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. *N Engl J Med* 1991;324:947-53.

Once-daily methimazole is more effective than once-daily propylthiouracil

Homansit M, Sriussadaporn S, Vannasaeng S, Peerapatdit T, Nitiytanat W, Vichayanrat A. Efficacy of single daily dosage of methimazole vs. propylthiouracil in the induction of euthyroidism. *Clin Endocrinol* 2001;54:385-90.

SUMMARY

Background Methimazole and propylthiouracil are both effective in reducing thyroid secretion in patients with hyperthyroidism. Between them, methimazole has a longer plasma half-life and a longer duration of action within the thyroid, suggesting that it can be given less often. This study was designed to determine the relative efficacy of single daily doses of methimazole and propylthiouracil in patients with hyperthyroidism.

Methods The study subjects were 71 patients (62 women, 9 men) with newly diagnosed hyperthyroidism caused by Graves disease living in Bangkok, Thailand. Their mean [\pm SD] age was 35 ± 12 years and their mean body weight was 53 ± 8 kg. The mean duration of symptoms of hyperthyroidism was 7 ± 7 months. After diagnosis, the patients were randomly assigned to receive 15 mg of methimazole or 150 mg of propylthiouracil once daily orally for 12 weeks. Serum thyroxine (T_4), triiodothyronine (T_3), and thyrotropin (TSH) were measured at baseline and again after treatment for 4, 8, and 12 weeks. The outcome variables were changes in these measurements, and no information about changes in symptoms or signs of hyperthyroidism or adverse effects of the drugs is provided.

Results There were 31 women and 4 men in the methimazole group and 31 women and 5 men in the propylthiouracil group. At baseline, the mean body weight, goiter size, and serum T_4 and T_3 concentrations were similar in the two groups.

The serum T_4 and T_3 concentrations declined more rapidly

in the methimazole group, so that the proportion of patients who were euthyroid was higher at all times in this group than in the propylthiouracil group (table). The proportion of patients who were hypothyroid also was higher in the methimazole group at all times.

Table. Changes in Thyroid Function during Treatment with Methimazole or Propylthiouracil.

	Baseline	Week 4	Week 8	Week 12
Serum T_3 (ng/dL)				
Methimazole	564	230	158	144
Propylthiouracil	536	357	305	280
Serum T_4 (μ g/dL)				
Methimazole	20.8	11.9	7.9	7.0
Propylthiouracil	21.4	14.6	13.7	12.7
Serum T_4 and T_3 normal (% of patients)				
Methimazole		31	63	77
Propylthiouracil		14	17	19
Hypothyroidism (% of patients)*				
Methimazole		9	26	31
Propylthiouracil		0	0	0

To convert serum T_3 values to nmol/l multiply by 0.01536, and to convert serum T_4 values to nmol/L multiply by 12.9. Normal ranges: serum T_4 , 5.0 to 12.4 μ g/dL (65 to 160 nmol/L; serum T_3 , 52 to 168 ng/dL (0.8 to 2.6 nmol/L). *Defined as a high serum TSH concentration or low serum T_4 concentration.

Conclusion Among patients with hyperthyroidism, a single daily dose of 15 mg of methimazole is more effective in reducing thyroid secretion than a single daily dose of 150 mg of propylthiouracil.

COMMENTARY

Several useful findings emerge from this study. One is that a relatively low dose of methimazole, given once daily, reduced serum T_4 and T_3 concentrations to normal in a relatively short interval, confirming previous studies that once-daily doses and low doses are nearly as effective as divided doses and high doses (and are safer) (1). Another is that 15 mg methimazole is considerably more potent than 150 mg of propylthiouracil, confirming a study in patients treated with 10 mg of methimazole or 100 mg of propylthiouracil, each given three times daily (2). Thus, the potency of methimazole is certainly more than 10

times that of propylthiouracil, the standard estimate. A third is that the ability of propylthiouracil to reduce extrathyroidal conversion of T_4 to T_3 is not evident after the first few days of treatment, because of the drug's poor antithyroid action. With respect to the dosing interval for propylthiouracil, in the only direct comparison, in 49 patients, 150 mg given three times daily was more effective than 450 mg given once daily (3). If once-daily therapy is preferable, and surely it is, then methimazole is the better antithyroid drug.

Robert D. Utiger, M.D.

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Liver disease in patients with hyperthyroidism treated with propylthiouracil

Kim H-J, Kim B-H, Han Y-S, Yang I, Kim K-J, Dong S-H, Kim H-J, Chang Y-W, Lee J-I, Chang R. The incidence and clinical characteristics of symptomatic propylthiouracil-induced hepatic injury in patients with hyperthyroidism: a single-center retrospective study. *Am J Gastroenterol* 2001;96:165-9.

SUMMARY

Background Propylthiouracil is known to be hepatotoxic, but the frequency of clinically important liver injury during propylthiouracil therapy in patients with hyperthyroidism is not known.

Methods Clinical manifestations of hepatitis jaundice, anorexia, nausea, vomiting, fever, pruritis or rash, and arthralgia were sought, and serum bilirubin, alkaline phosphatase, alanine aminotransferase and other hepatic enzymes were measured before treatment and again two and four weeks and then every few months after the initiation of propylthiouracil therapy in 497 Korean patients (357 women and 140 men; mean age 43 years; range, 16 to 75) with hyperthyroidism. At baseline, all the patients had serum bilirubin, alanine and aspartate aminotransferase, and alkaline phosphatase concentrations not more than two times the upper limit of normal, and none had a history of hepatic or biliary tract disease. During the same period (1990 to 1998), 415 other patients with hyperthyroidism were treated at the same center; 291 underwent thyroidectomy, 81 had congestive heart failure, and 43 had abnormal liver function or were taking possibly hepatotoxic drugs.

In patients with evidence of hepatic disease, the drug was discontinued, and additional tests were done to exclude other causes of hepatitis. Liver biopsies were not done. The patients were then followed until their liver function was normal, after which they were treated with radioactive iodine or methimazole.

Results Six patients (1.2 percent) developed clinically

apparent liver disease, characterized by jaundice and pruritis in 5 patients, fever and rash in 2 patients and arthralgia in 1 patient, 12 to 49 days (mean, 29) after the initiation of propylthiouracil therapy (300 to 450 mg daily). All 6 patients had high serum alkaline phosphatase concentrations, 5 had high serum bilirubin concentrations, and 4 had high serum alanine aminotransferase concentrations. Based on standard criteria, 3 patients were considered to have cholestatic hepatitis, 2 patients mixed hepatocellular and cholestatic hepatitis and 1 patient hepatocellular hepatitis. After propylthiouracil therapy was discontinued, the patients serum alanine aminotransferase concentrations fell to normal in an average of 30 days (range, 13 to 57) and their serum bilirubin concentrations fell to normal in an average of 73 days (range, 16 to 145) days. The patients who developed hepatitis did not differ from those who did not in age, estimated duration of hyperthyroidism, pretreatment serum thyroxine or triiodothyronine concentrations, or initial dose of propylthiouracil.

In addition to these 6 patients, 71 patients (14.3 percent) had high serum alanine aminotransferase concentrations, but no symptoms of hepatitis, 25 to 120 days (mean, 75) after the initiation of propylthiouracil therapy. The mean (\pm SD) peak value was 60 ± 17 U/L, and the values returned to normal in all patients despite continued propylthiouracil therapy.

Conclusion Propylthiouracil caused symptomatic hepatitis in 1.2 percent of patients treated with the drug. The presence of fever, rash, and arthralgia suggest that the hepatitis was caused by a hypersensitivity reaction rather than drug toxicity.

COMMENTARY

This is the most comprehensive study of the effects of propylthiouracil on liver function and therefore the most realistic estimate of the likelihood of overt hepatotoxicity during therapy with the drug yet published. The 1.2 percent frequency of hepatitis could be an underestimate, because after two months of treatment liver function was assessed erratically and the duration of treatment is not stated. Until now, all the information on propylthiouracil-associated hepatotoxicity came from case reports; in a review published in 1997 the authors were able to identify 27 reasonably well documented cases from the literature (1966-1996) and added 2 more (1). Of these 29 patients, 22 survived (2 under-

went liver transplantation) and 7 died.

Ten times more patients (14.3 percent) had small increases in serum alanine aminotransferase concentrations that did not persist despite continued treatment. In the only other systematic study of liver function in patients with hyperthyroidism treated with propylthiouracil, done in Taiwan, 15 of 54 patients (27.8 percent) had similar small transient asymptomatic increases in serum alanine aminotransferase concentrations after treatment for 2 months (2).

The exclusion of patients with more than a minor degree of hepatic dysfunction at baseline was reasonable from the viewpoint of the study, but information about their risk of propylthiouracil-induced hepatotoxicity would be useful. Finally, is the risk of either

minimal or more severe propylthiouracil-induced hepatic dysfunction the same in non-Asians as in Asians?

Robert D. Utiger, M.D.

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Hypothyroidism is associated with plasma hypo-osmolality and impaired water excretion that is vasopressin-independent

Sahun M, Villabona C, Rosel P, Navarro MA, Ramon JM, Gomez JM, Soler J. Water metabolism disturbances at different stages of primary thyroid failure. *J Endocrinol* 2001;168:435-45.

SUMMARY

Background Occasional patients with hypothyroidism have hyponatremia and water intoxication, but whether the changes are due to hypothyroidism per se and are caused by excess vasopressin secretion or renal tubular dysfunction are controversial. This study was undertaken in an attempt to clarify the effect of hypothyroidism on the regulation of water metabolism.

Methods The plasma and urinary responses to water loading and hypertonic saline infusion were studied in 16 patients (12 women and 4 men; mean age, 44 years) with overt primary hypothyroidism before and during treatment with thyroxine, 8 patients (all women; mean age, 38 years) with subclinical hypothyroidism, and 16 normal subjects (14 women and 4 men; mean age, 42 years). The group mean serum thyrotropin (TSH) concentrations were 129, 3.8, 13.5, and 1.7 mU/L, respectively. Patients with diabetes mellitus and cardiac, renal, hepatic, and adrenal disease and those taking drugs that alter water and sodium homeostasis were excluded.

The oral water-loading test consisted of ingestion of 20 mL/kg of water in 30 minutes after an overnight fast. The hypertonic saline infusion test consisted of intravenous infusion of 3 mL/kg/hour of 5 percent saline for 120 minutes. Plasma osmolality, vasopressin, atrial natriuretic hormone, renin and aldosterone, and urinary volume and osmolality were measured at regular intervals for 240 minutes after water loading and for the duration of the saline infusion.

Results Baseline plasma osmolality and plasma vasopressin concentrations were slightly lower (by approximately 5 to 7 mOsm/kg and 0.6 pg/mL [0.6 pmol/L], respectively) in the patients with overt hypothyroidism, as compared with the normal subjects, but urine osmolality was similar.

After water loading, the patients with hypothyroidism and the normal subjects excreted at least 80 percent of the water load. Plasma osmolality and plasma vasopressin concentrations decreased similarly in the patients with overt hypothyroidism and the normal subjects, but changed less in the other groups. Urine osmolality decreased in parallel in all groups, but free water clearance increased less in the patients with overt hypothyroidism than in the normal subjects.

During the saline infusion, the basal and final urine osmolality and the changes in urine volume, sodium excretion, and water and osmolal clearance were similar in the four groups. Plasma osmolality and plasma vasopressin concentrations increased in all groups, but were lower at all times in the patients with overt hypothyroidism and at some times in the patients with subclinical hypothyroidism, as compared with the normal subjects.

There were no differences in plasma renin activity or plasma aldosterone or atrial natriuretic hormone concentrations in any of the groups either before or during water loading or hypertonic saline infusion.

Conclusion Patients with hypothyroidism have vasopressin independent plasma hypo osmolality.

COMMENTARY

These are not easy results to summarize, given the multiple measurements during two tests in four groups of patients, but the overall findings seem clear. The patients with overt but uncomplicated hypothyroidism had slightly lower plasma osmolality values, as compared with the normal subjects, which were not caused by inappropriate vasopressin secretion because they had low plasma vasopressin concentrations. Furthermore, vasopressin secretion was further decreased appropriately by water loading and increased - also appro-

priately - by hypertonic saline infusion. The abnormalities that cause the plasma hypo-osmolality and the decrease in free water clearance after water loading must therefore lie in the kidneys.

Given the minimal decreases in plasma osmolality in the patients with overt hypothyroidism, their plasma sodium concentrations, which were not reported, would not be expected to be low. In fact, hyponatremia must be very rare in patients with hypothyroidism. In a survey of 33,192 patients from a large city hospital, the distribution of serum sodium concentrations was the same in patients with normal and high

(>40 mU/L) serum TSH concentrations (1). When hyponatremia occurs in hypothyroidism, there must be complicating factors.

Robert D. Utiger, M.D.

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Estrogen increases the requirement for thyroxine in women with hypothyroidism

Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med* 2001;344:1743-9.

SUMMARY

Background Women with hypothyroidism are known to need higher doses of thyroxine (T₄) to maintain normal serum thyrotropin (TSH) concentrations when they are pregnant. Possible causes of this increased need for T₄ are higher serum thyroxine-binding globulin (TBG) concentrations, caused by increased estrogen production; loss of T₄ to the fetus; and placental conversion of T₄ to reverse triiodothyronine. This study was undertaken to determine whether the increase in serum TBG concentrations induced by estrogen alone increase the need for T₄ in women with hypothyroidism.

Methods The study subjects were 36 postmenopausal women for whom estrogen therapy was indicated. Eleven had normal thyroid function, 18 had hypothyroidism and were receiving long-term T₄ replacement therapy (mean dose 104 µg/day), and 7 had been treated for thyroid carcinoma and were receiving long-term T₄ suppression therapy (mean dose, 138 µg/day). The women continued their usual dose of T₄ and were treated with 0.625 mg conjugated estrogens, and intermittent medroxyprogesterone acetate if they had not had a hysterectomy, for 48 weeks. Serum T₄, free T₄, TBG, and TSH were measured at 6-week intervals in all the women. The dose of T₄ was increased in women in the T₄-replacement group if their serum TSH concentration increased above 7 µU/mL and in the women in the T₄-suppression group if their serum TSH concentration increased above 1 µU/mL, and their subsequent data were excluded.

Results At baseline, the normal women and the women in the T₄-replacement group had similar serum T₄, free T₄, and

TSH concentrations, whereas the women in the T₄-suppression group had higher serum T₄ and free T₄ and lower serum TSH concentrations. In all groups, serum TBG and T₄ concentrations increased in 6 weeks and reached a peak in 12 weeks, after which they did not change (table). Serum free T₄ concentrations did not change in the normal women, but decreased in both groups of women with hypothyroidism.

Table. Serum TBG, T₄, and Free T₄ Concentrations in Estrogen-Treated Women with Hypothyroidism Treated with Estrogen.

Study group	Serum TBG (mg/L)		Serum T ₄ (µg/dL)		Serum Free T ₄ (ng/dL)	
	Baseline	12 Weeks	Baseline	12 weeks	Baseline	12 weeks
Normal women (n=11)	20.3	31.3*	8.0	10.4*	1.2	1.1
T ₄ -replacement (n=18)	20.8	30.8*	8.3	10.9*	1.5	1.2*
T ₄ -suppression (n=7)	20.7	30.8*	11.0	14.5*	2.1	1.7*

To convert serum T₄ and free T₄ values to nmol/L and pmol/L, respectively, multiply by 12.9.
*P<0.01 or less.

Serum TSH concentrations did not change in the normal women. Seven women in the T₄-replacement group had increases in serum TSH concentrations to >7 µU/mL and 3 women in the T₄-suppression group had increases to >1 µU/mL, and their T₄ doses were raised.

Conclusion Women with hypothyroidism may need more T₄ when treated with estrogen.

COMMENTARY

These results indicate that an increase in TBG production alone, independent of other changes in thyroid homeostasis that occur in pregnant women, can lead to an increased T₄ requirement in women with hypothyroidism. As compared with pregnant women, it appears that fewer estrogen-treated women need more T₄ and also that the increase in need is less, as extrapolated from the increases in serum TSH values reported (data on the increases in T₄ doses needed to restore TSH secretion to normal are not included). Corollaries of these results are that women taking estrogen who are then

given T₄ may need a slightly higher dose than if they were not taking estrogen, and discontinuing estrogen in women taking both estrogen and T₄ could induce mild hyperthyroidism.

Changes in serum TBG concentrations are something to be reckoned with in treating patients with thyroid disease. But what does TBG do in normal subjects, and what are the physiological consequences of changes in serum TBG concentrations in them? The simple answer to both questions seems to be nothing. Clinically, men with TBG gene deletions (the gene is X-linked), in whom serum TBG concentrations are undetectable, and those with two-fold increases in serum TBG concentrations, due to

duplication of the TBG gene, are euthyroid and have normal serum free T₄ and TSH concentrations, just as do people with estrogen-induced increases in serum TBG concentrations. TBG could serve as a circulating reservoir of T₄ and T₃, providing the hormones to tissues almost instantaneously, or as a buffer, protecting tissues from surges of thyroid secretion or egress of T₄ or T₃ from tissues, but neither of these situations is known to occur. It may also serve to distribute T₄ or T₃ more evenly within large organs, but the plausibility of this mechanism is belied by the normality of men with complete TBG deficiency.

Robert D. Utiger, M.D.

Radioiodine is more effective than thyroxine in decreasing goiter size in patients with nodular goiter

Wesche MFT, Tiel-v Buul MMC, Lips P, Smits NJ, Wiersinga WM. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. *J Clin Endocrinol Metab* 2001;86:998-1005.

SUMMARY

Background Patients with a sporadic nontoxic nodular goiter called sporadic because the patients live in an area of iodine sufficiency are often treated with thyroxine (T_4) to reduce the size of their goiter, although it is little more effective than a placebo. In contrast, iodine-131 (I-131) has proven effective in reducing goiter size in uncontrolled studies. The purpose of this study was to compare the effects of T_4 and I-131 in a relatively homogeneous group of patients with nontoxic nodular goiter living in an area where iodine intake is sufficient.

Methods Sixty four patients with nontoxic nodular goiter were randomly assigned to treatment with I-131 or daily T_4 and followed at regular intervals for 2 years. There were 31 women, of whom approximately half were peri- or postmenopausal, and 2 men in each group. Patients with cardiac disorders or severe obstructive symptoms were excluded, but most patients had some symptoms referable to their goiter. The diagnosis was based on demonstration of one or more nodules by ultrasonography (with biopsies negative for thyroid cancer when appropriate) and on technetium (Tc)-99m scans that revealed heterogeneous uptake. Other baseline characteristics of the I-131 and T_4 groups, respectively, were: mean age, 49 and 50 years; multinodular goiter, 30 and 29 patients; and median thyroid volume, 60 mL (range, 17 to 198) and 57 mL (range, 18 to 260). The patients had normal serum T_4 and triiodothyronine concentrations; their median serum thyrotropin (TSH) concentrations were 0.6 mU/L (I-131 group) and 0.8 mU/L (T_4 group) (normal, 0.4 to 4.0), but 10 patients in the I-131 group and 7 patients in the T_4 group had low serum TSH concentrations.

In the I-131 group the goal of treatment was to deliver 4.44 MBq (120 μ Ci)/mL of thyroid tissue, and the administered doses ranged from 444 to 3330 MBq (12 to 90 mCi); T_4 was given to patients who had high serum TSH concentrations during follow-up. In the T_4 group the initial dose was 2.5 μ g/kg/day, and the dose was adjusted to maintain serum TSH concentrations between 0.01 and 0.1 mU/L or serum free T_4 concentrations within the upper limit of the normal range. The primary endpoints of the study were goiter size at 1 and 2 years; a secondary endpoint was lumbar spine and hip mineral density at 1 and 2 years.

Results In the 29 patients in the I-131 group who completed the study, thyroid volume decreased to 36 mL (range, 4 to 130) after 1 year and to 30 mL (range, 6 to 165) after 2 years; the mean decreases were 38 percent and 44 percent, respectively. In contrast, in the 28 patients in the T_4 group who completed the study the median thyroid volume decreased to 54 mL (range, 18 to 243) after 1 year and it was 60 mL (range, 20 to 287) after 2 years; the mean decreases were 7 percent and 1 percent, respectively. More patients in the I-131 group had improvement in symptoms, and their serum TSH concentrations increased approximately 3-fold. In the T_4 group, the mean serum TSH concentration was 0.02 mU/L after 1 and 2 years, and some patients had symptoms of hyperthyroidism. Lumbar spine density did not change in the I-131 group but decreased in the T_4 group, whereas hip density did not change in either group.

Conclusion In patients with sporadic goiter, I-131 is considerably more effective than T_4 in decreasing goiter size and ameliorating goiter-related symptoms, and it does not cause loss of bone.

COMMENTARY

This study provides compelling evidence that I-131 is far more effective than T_4 in reducing thyroid size in patients with nontoxic nodular goiter, and it does so without causing subclinical hyperthyroidism. These results confirm those of several uncontrolled studies of I-131 (summarized in ref. 1), and indeed should put to rest the notion that T_4 has any value in these patients. The inclusion of a few patients with a uninodular goiter was unfortunate, because that is probably a different disorder, but it does not detract appreciably from the overall results.

The mean decrease in thyroid volume in these studies was approximately 50 percent in the first year after treatment, with little additional increase thereafter, but approximately 20 percent of patients had little decrease or even an increase in goiter size. A few patients have radiation thyroiditis soon after treatment, some later become hypothyroid, and a few develop Graves' hyperthyroidism, presumably a result of autoimmunization (1). If compressive symptoms are prominent, then I-131 therapy is no match for thyroidectomy. If they are not, and treatment is indicated to reduce goiter size or ameliorate

subclinical hyperthyroidism, then I-131 should be given.

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Galectin-3 is a sensitive and specific cellular marker of thyroid carcinoma

Bartolazzi A, Gasbarri A, Papotti M, Bussolati G, Lucante T, Khan A, Inohara H, Marandino F, Orlandi F, Nardi F, Vecchione A, Tecce R, Larsson O, and the Thyroid Cancer Study Group. Application of an immunodiagnostic method for improving diagnosis of nodular thyroid lesions. *Lancet* 2001;357:1644-50.

SUMMARY

Background The wide usage of fine-needle aspiration biopsy in patients with thyroid nodules has led to improved diagnosis and has spared many patients unnecessary surgery, but the results are nondiagnostic in some patients, in particular those with follicular lesions. Galectin-3 is a cell-surface protein involved in cell-cell and cell-matrix interactions that has been associated with thyroid carcinomas in small studies. CD44 is a molecule with similar properties that is expressed on normal thyroid cells, but a variant form, CD44v6, has been associated with thyroid carcinomas. This study was undertaken to determine if the presence of galectin-3 and CD44v6 in thyroid nodules predicted the presence of thyroid carcinoma.

Methods The presence of galectin-3 and CD44v6 was determined by immunohistochemical methods using highly specific monoclonal antibodies in formalin-fixed tissue sections from 618 thyroid lesions removed previously, and in fresh samples obtained by fine-needle aspiration biopsy of thyroid nodules in 226 patients, all of whom subsequently underwent surgical excision of their nodules. The results in each group were correlated with the histopathological findings. The immunostaining and histopathological evaluations were done by different pathologists. The studies were done at six different institutions, with good agreement in the findings. The results of the analyses for CD44v6 were less sensitive and specific for the detection of thyroid carcinoma, and will not be presented below.

Results Among the thyroid lesions studied retrospectively, none of the 75 specimens classified as normal thyroid tissue contained galectin-3. Among the 212 specimens classified as

benign, which included adenomatous nodules, autoimmune thyroiditis, and benign adenomas, 205 (97 percent) were negative for galectin-3. Among the 331 thyroid carcinomas, 307 (93 percent) contained galectin-3; most of the carcinomas that were negative were anaplastic or other poorly differentiated carcinomas. Among the 57 follicular lesions that met histopathological criteria for carcinoma (vascular or capsular invasion), 54 (95 percent) were positive for galectin-3, as compared with 4 of 125 (3 percent) of nodules that proved to be follicular adenomas. The sensitivity and specificity of galectin-3 immunostaining for the detection of thyroid carcinomas were 94 percent and 98 percent, respectively. The results of the studies of cell blocks were similar.

The results in the 226 patients studied prospectively also were similar. Among them, 153 had adenomatous nodules or thyroiditis, of which only 1 nodule (0.6 percent) was positive for galectin-3. Based on cytological evaluation 82 of these 226 nodules (36 percent) were considered follicular lesions. Based on histopathological evaluation, 39 patients had follicular adenomas, of which 2 (5 percent) were positive for galectin-3, and 28 patients had papillary or follicular carcinomas, all of which were positive for galectin-3. Thus, the sensitivity and specificity of galectin-3 immunostaining for the detection of papillary and follicular carcinomas on the cytological specimens were 100 percent and 98 percent, respectively (there were no anaplastic carcinomas in this group).

Conclusion The presence of galectin-3 in thyroid nodules and thyroid cells obtained by fine-needle aspiration biopsy accurately predicts the presence of papillary and follicular thyroid carcinomas.

COMMENTARY

The presence of galectin-3 seems to be both a sensitive and specific indicator of the presence of carcinoma of thyroid epithelial cells, either papillary or follicular carcinoma, whatever the importance of the molecule in tumor biology. Examination of cytological specimens for galectin-3 may be particularly useful in evaluating patients with follicular tumors, because at present there is no reliable way to distinguish between follicular adenomas and follicular carcinomas except by careful examination of permanent sections of surgically removed tissue looking for vascular or

capsular invasion. A study describing the lack of value of examination of frozen sections of tissue obtained during surgery in patients with these tumors is described on page 31 in this issue. Follicular carcinomas can be differentiated from follicular adenomas by the presence of a PAX8-PPAR γ 1 fusion gene in the carcinomas, as discussed in the previous issue of this journal, but not all follicular carcinomas have this molecular abnormality (1).

There is less need for improved methods to identify papillary carcinomas, because their unique nuclear characteristics make them relatively easy to recognize in cytological specimens. Nonetheless, some biopsies are reported

to be suggestive of papillary carcinoma, and for those patients further evaluation of their biopsies with a reliable marker of carcinoma would likely spare some an operation.

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Low value of intraoperative frozen sections in patients with follicular neoplasms

Udelsman R, Westra WH, Donovan PI, Sohn TA, Cameron JL. Randomized prospective evaluation of frozen-section analysis for follicular neoplasms of the thyroid. *Ann Surg* 2001;233:716-22.

SUMMARY

Background Benign and malignant thyroid follicular-cell tumors, including Hurthle-cell tumors, are difficult if not impossible to identify correctly on the basis of their cytological characteristics. Based on the results of fine-needle aspiration biopsies, these nodules are often designated follicular neoplasms or tumors. The patients are usually advised to have surgery because approximately 10 to 20 percent of the nodules are follicular carcinomas. The extent of surgery is often determined by the results of analysis of frozen sections of the nodule, in particular by the presence of cellular invasion of vessels or the capsule indicative of carcinoma. Often, however, these findings are detected only after analysis of permanent sections. This study was undertaken to examine prospectively the value of frozen-section analysis in patients with follicular neoplasms.

Results The study subjects were 61 patients with thyroid nodules in whom fine-needle aspiration biopsies revealed a follicular neoplasm. At surgery, after exploration had revealed no local or lymph-node invasion by tumor and a normal contralateral thyroid lobe, the patients were randomly assigned to have or not to have the nodule examined by frozen section. Then the thyroid lobe containing the nodule and the isthmus were removed. In patients assigned to the frozen-section group, sections of the tumor were frozen and examined immediately. If analysis of the frozen sections revealed follicular carcinoma, the contralateral lobe was removed. In patients in whom the frozen sections were read as a benign nodule but the permanent sections were read as follicular carcinoma, the contralateral thyroid lobe was removed later.

Results The characteristics of the patients in the frozen-section and no-frozen-section groups were similar. In the

frozen-section group, the frozen sections revealed follicular carcinoma in only 1 patient; the diagnosis was confirmed by analysis of permanent sections. In this group, analysis of permanent sections revealed follicular carcinoma in 6 more patients (table). In the no-frozen-section group, 1 patient was thought to have carcinoma on the basis of analysis of the lobectomy specimen, confirmed by analysis of frozen and permanent sections, and was termed a conscious protocol violation. Among the other 31 patients in the no-frozen-section group, the permanent sections revealed carcinoma in 3 patients; 1 was a follicular carcinoma, 1 a Hurthle-cell carcinoma, and 1 a follicular variant of papillary carcinoma.

Table. Characteristics of Patients with Thyroid Nodules and Results of Analysis of Frozen and Permanent Sections of the Nodules.

	Frozen-Section Group n=29	No-Frozen-Section Group n=32
Women (%)	79	69
Mean age (yr)	40	43
Mean diameter of nodule (cm)	3.1	2.8
Carcinomas		
Frozen-section (%)	1(3.4)	0 (0)*
Permanent-section (%)	7 (24.1)	4 (12.5)*

*Including the patient in whom examination of the lobectomy specimen revealed transcapsular invasion.

The mean anesthesia time, operative time, hospital stay and total hospital charges in the two groups were similar. The mean charge for the 1 informative frozen section in the 29 patients in the frozen-section group was \$12,470.

Conclusion Analysis of frozen sections of thyroid nodules in patients with follicular neoplasms is not useful.

COMMENTARY

The results of this prospective study provide further evidence that analysis of frozen sections of thyroid nodules classified as follicular neoplasms has little value, confirming the results of retrospective studies (1). The problem is simply that it is extremely difficult to distinguish between benign and malignant follicular neoplasms in a few sections of frozen tissue, because of distortion of the tissue and the difficulty in identifying vascular or capsular invasion, the hallmarks of follicular carcinoma.

One solution to this problem is to do a near-total thyroidectomy in all patients with a follicular neoplasm, on the basis that the nodule is a follicular carcinoma. That seems inappropriate, given the relative infrequency of follicular carcinomas among nodules classified as follicular neoplasms on the basis of cytological examination. Recent studies suggest that it may be possible to distinguish between benign and malignant follicular tumors on the basis of molecular characteristics (2), but until one of these procedures is validated these patients should be treated initially by lobectomy,

contralateral lobectomy being done later if the nodule proves to be malignant.

Robert D. Utiger, M.D.

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Salivary and lacrimal gland dysfunction after radioiodine therapy

Solans R, Bosch J-A, Galofre P, Porta F, Rosello J, Selva-O Callagan A, Vilardell M. Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy. *J Nucl Med* 2001;42:738-43.

SUMMARY

Background The salivary glands, like thyroid tissue, have sodium-iodide transporters and therefore concentrate inorganic iodine from the plasma. In some patients with thyroid carcinoma who are treated with iodine-131 (I-131), sufficient radioactivity accumulates in the parotid and submandibular glands to cause acute or chronic sialadenitis. This study was undertaken to determine prospectively the frequency of salivary gland and lacrimal gland dysfunction after I-131 therapy in patients with thyroid carcinoma.

Methods The study subjects were 79 consecutive patients (68 women and 11 men; mean age, 46 years; range, 22 to 80) who were treated with I-131 between 1990 and 1995. Among them, 65 had papillary carcinoma, 11 had follicular carcinoma, 2 had toxic multinodular goiters, and 1 was not stated. The doses of I-131 ranged from 25 to 500 mCi (925 MBq to 18.5 GBq); 46 patients (58 percent) received 100 mCi (3.7 GBq). The patients were advised to increase their fluid intake and chew gum to increase salivary flow after I-131 treatment. The patients were questioned systematically about symptoms of salivary gland dysfunction—dry mouth, gingivitis, parotid pain or enlargement, loss of taste and difficulty swallowing dry foods (xerostomia) and lacrimal gland dysfunction—dryness, burning and redness of the eyes, conjunctivitis and photosensitivity (xerophthalmia) before and at yearly intervals for 3 years after I-131 therapy. Salivary gland function was assessed by frequent scanning for 60 minutes after intravenous injection of technetium (Tc)-99m, and lacrimal gland function was assessed by the Schirmer test, also yearly for 3 years.

Results The numbers of patients reporting xerostomia

1, 2 and 3 years after I-131 therapy were 26 (33 percent), 16 (20 percent), and 12 (15 percent), respectively; none of the patients in year 2 and 2 of the patients in year 3 had not had symptoms before. The most common symptoms were dry mouth and abnormal taste, which usually began several weeks after treatment and persisted for several weeks, if not longer. Four patients (5 percent) had oral ulcers, and 16 (20 percent) had sialadenitis. This involved the parotid glands in 10 patients and the submandibular glands in 6, and was treated with a nonsteroidal anti-inflammatory drug. The salivary scans were abnormal, with delayed uptake and delayed excretion in 40 patients (51 percent) at 1 year, 14 patients (18 percent) at 2 years (including 11 patients with a previously abnormal scan), and 39 patients (49 percent) at 3 years (also including 11 patients with a previously abnormal scan).

The numbers of patients reporting xerophthalmia 1, 2 and 3 years after I-131 therapy were 20 (25 percent), 14 (18 percent) and 11 (14 percent), respectively. The Schirmer tests were abnormal in 14 patients (18 percent) at 1 year, 11 patients (14 percent) at 2 years, and 6 patients (8 percent) at 3 years.

In general, patients who received higher doses of I-131 were more likely to have xerostomia and xerophthalmia, and all patients who had xerophthalmia also had xerostomia. Patients who had subjective xerostomia usually had objective xerostomia as well, but that was not the case for xerophthalmia.

Conclusion Patients given high doses of I-131 may have xerostomia and xerophthalmia that persists for several years after treatment.

COMMENTARY

Sialadenitis is a well-recognized side effect of high-dose I-131 therapy, and is presumably caused by radiation-induced inflammation of salivary tissue. The results of this prospective study document not only the occurrence but also the persistence of salivary gland dysfunction after high-dose I-131 therapy. The most common symptoms of salivary dysfunction were dry mouth and abnormal taste sensation, but the other symptoms comprising xerostomia were not separately tabulated. Unfortunately the paper contains no information about I-131 uptake by thyroid tissue; in another

study salivary gland dysfunction was inversely related to thyroid uptake (1).

Lacrimal tissue contains sodium-iodide transporters, although I-131 has been detected in tears (2), and chronic conjunctivitis has been reported as a side effect of high-dose I-131 therapy (1). One explanation for the conjunctivitis gland dysfunction might be the induction of autoimmune lacrimal gland dysfunction (Sjögren's syndrome). To address this possibility the authors measured serum anti-DNA antibodies before and after treatment; 9 patients had positive tests at 1 year, of whom only 2 had a positive test at 3 years, but whether they had xerostomia or xerophthalmia is not stated. Tests for other antibodies

(anti-La and anti-Ro) associated with Sjögren's syndrome were negative.

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Fluorodeoxyglucose scanning can provide useful information in patients with recurrent thyroid cancer

Schluter B, Bohuslavizki KH, Beyer W, Plotkin M, Buchert R, Clausen M. Impact of FDG PET on patients with differentiated thyroid cancer who present with elevated thyroglobulin and negative ¹³¹I scan. *J Nucl Med* 2001;42:71-6.

SUMMARY

Background Some previously treated patients with thyroid carcinoma have high serum thyroglobulin concentrations but no tumor is detected by diagnostic whole-body scanning with iodine-131 (I-131) or -123 (I-123). These patients are presumed to have recurrent or metastatic carcinoma, which can sometimes be identified by scanning 3 to 7 days after administration of a high (therapeutic) dose of I-131 (post-therapy scan) or by other radionuclide and non-radionuclide scanning procedures. Among the former is F-18-fluorodeoxyglucose (FDG), which can be detected by positron-emission scanning. FDG scanning takes advantage of the fact that many tumors, even differentiated thyroid carcinomas, take up and utilize glucose more rapidly than normal tissue.

Methods The utility of FDG scanning was evaluated in 64 patients (39 women and 25 men; age range, 21 to 81 years) with differentiated thyroid carcinoma who were suspected to have recurrent or metastatic carcinoma. The carcinomas were not otherwise defined. Among the 64 patients, who were studied after discontinuation of thyroxine therapy, 48 (75 percent) had high serum thyroglobulin concentrations and negative diagnostic whole-body I-131 scans, 7 (11 percent) had high serum thyroglobulin concentrations and positive diagnostic I-131 scans but were suspected to have tumor in other locations, and 9 patients (14 percent) had low serum thyroglobulin concentrations but evidence of recurrent carcinoma as determined by ultrasonography, computed tomography, or other non-radionuclide scans. After fasting for 12 hours the patients were given 370 MBq (10 mCi) of FDG intravenously and underwent whole-body scanning 60 minutes later. The results of the FDG scans

were compared with those of other imaging procedures and, in some patients, with the cytology or histology of biopsies of suspected tumor masses. The follow-up interval ranged from 1 to 64 months.

Results Among the 64 patients, 44 had positive FDG scans. Two patients proved to have nonthyroid tumors and 1 had true positive, false positive and false negative findings. The results in the remaining 41 patients are shown in the table.

FDG Scan	No.	Cytology- Histology	Positive I-131 Scan	Positive CT or MR Scan	Low Serum Thyroglobulin Later
True-positive	34	17	8	9	0
False-positive	7	3	0	2	2
True-negative	5	0	0	0	5
False-negative	15	2	1	1	11

In the 34 patients in the true positive group the FDG scan results led to additional treatment in 19 patients (18 surgery, 10 I-131 therapy, and 4 external radiation therapy); 7 patients had widespread thyroid carcinoma and received only palliative treatment. The 7 patients in the false-positive group had no other evidence of thyroid carcinoma despite extensive study and follow-up. The 15 patients in the false negative group all had evidence of recurrent carcinoma on the basis of other studies.

Conclusion In some patients with thyroid carcinoma whose tumors do not concentrate I-131 scanning with FDG identifies recurrent or metastatic tumor and may alter therapy.

COMMENTARY

Most recurrences or metastases in patients with differentiated (papillary or follicular) thyroid carcinoma are detected after the patients are found to have a high serum thyroglobulin concentration while taking or after discontinuation of thyroxine therapy, or they have a tumor mass in the neck or elsewhere. Then, a diagnostic whole-body I-131 or I-123 scan is done. It reveals uptake somewhere, including in any already detected tumor masses, in from 70 to 90 percent of the patients. In the remainder, the options are to administer a therapeutic dose of I-131, for example 200 mCi (7400 MBq), or to undertake a search for tumor using other techniques.

If a high dose of I-131 is given, a post-therapy scan will reveal tumor in most of the patients, and serum thyroglobulin concentrations will fall in some of them. The other techniques used for scanning include ultrasonography of the neck, chest or total-body CT or MR scans, or FDG, thallium-201, and indium-111 pentetreotide scans (1). Among the radionuclide tests, FDG scanning may reveal tumor more often than the others, but direct comparisons have not been performed. FDG scanning requires special equipment and is expensive, does not require cessation of thyroxine therapy, and identifies more metabolically active, and perhaps more aggressive, tumors (2). It is not clear that any additional therapy that may result from identification of

more tumor by FDG or other non-iodine scanning improves survival, but it may reduce morbidity.

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Good prognosis of patients with non-Hodgkin s lymphoma localized to the thyroid gland

Ha CS, Shadle KM, Medeiros LJ, Wilder RB, Hess MA, Cabanillas F, Cox JD. Localized non-Hodgkin lymphoma involving the thyroid gland. *Cancer* 2001;91:629-35.

SUMMARY

Background Most lymphomas of the thyroid gland are non-Hodgkin s lymphomas, and when confined to the thyroid the prognosis is usually very good. This study was undertaken to determine the natural history and efficacy of treatment in a large group of patients with non-Hodgkin s lymphoma localized to the thyroid gland, many of whom were treated with both chemotherapy and radiation therapy.

Methods The study subjects were 51 patients (33 women and 18 men; median age at the time of diagnosis, 59 years [range, 16 to 84]) with non-Hodgkin s lymphoma localized to the thyroid gland (Ann Arbor Stage I, 21 patients) or the thyroid gland and regional lymph nodes, including mediastinal lymph nodes (Ann Arbor Stage II, 30 patients) treated at one center from 1959, when megavoltage radiation therapy was introduced, to 1994. Nearly all of the patients had intermediate or high-grade lymphomas; the most common pathological diagnoses were diffuse large-cell lymphoma, found in 30 patients; follicular and diffuse large-cell lymphoma, 7 patients; immunoblastic plasmacytoid lymphoma, 4 patients; and follicular large-cell lymphoma, 3 patients. The diagnoses were established by thyroidectomy or biopsy.

Four patients were treated by thyroidectomy alone, 18 by thyroidectomy and radiation therapy, 5 with chemotherapy alone, and 24 by combined chemo- and radiation therapy. The median radiation dose was 42 Gy (range, 8 to 61), and the chemotherapy was cyclophosphamide, doxorubicin, vincristine, and prednisone in 21 patients and 3 of the 4 drugs in the remainder, given for a median of 7 cycles (range, 1 to 13).

Results The presenting manifestation of the thyroid lymphoma was a rapidly enlarging neck mass in 38 patients (74 percent) and symptoms referable to compression of neck structures in the remainder. Eight patients had a history of hypothyroidism, and none had a history of hyperthyroidism. The median follow-up was 10 years (range, 1 month to 26 years). All but one patient had a complete response to therapy, defined as no symptoms or signs of tumor. The overall survival rate was 64 percent at 5 years and 49 percent at 10 years; the rates in the patients with Stage I disease were 80 percent and 55 percent, respectively, and the rates in the patients with Stage II disease were 53 percent and 45 percent, respectively. The overall failure-free survival rates were 76 percent at both 5 and 10 years.

At both 5 and 10 years, the failure-free survival rates in the patients treated with radiation therapy were 76 percent and the failure-free survival rates in the patients treated with chemotherapy and radiation therapy were 91 percent. Neither sex, stage, mediastinal involvement nor treatment predicted the failure-free survival rates. Four of the 18 patients (22 percent) treated with radiotherapy had a recurrence, which was distant in most patients, as compared with 2 of the 24 patients (8 percent) treated with chemotherapy and radiation therapy.

Conclusion Patients with non-Hodgkin s lymphoma localized to the thyroid or thyroid and regional lymph nodes have a good prognosis, especially when treated with chemotherapy and radiation.

COMMENTARY

Malignant lymphomas constitute at most 2 percent of all malignant thyroid tumors, and among patients with primary extranodal lymphomas at most 2 percent originate in the thyroid gland. Virtually all thyroid lymphomas are B-cell tumors, based on immunophenotyping, and they are grouped together with lymphomas that originate in non-lymphoid tissue as lymphomas derived from mucosa-associated lymphoid tissue (MALT) or extranodal lymphoid tissue. These are tumors that arise in tissues prone to accumulate lymphocytes and in which lymphocyte proliferation is common (1).

This is exemplified in the case of the thyroid by the high frequency of clinical and pathological evidence of chronic autoimmune thyroiditis in patients with thyroid lymphomas (2), although nothing more than hypothyroidism is mentioned in this paper.

Many thyroid lymphomas are diffuse large-cell lymphomas, but other cell types can be found, as in this study. However, thyroid lymphomas are sufficiently rare that it is not possible to relate tumor type to prognosis. Most patients are treated with chemotherapy and radiation, with high, but not 100 percent, remission and survival rates.

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Limitation of serum thyrotropin measurements in evaluating thyroid function

Wardle CA, Fraser WD, Squire CR. Pitfalls in the use of thyrotropin concentration as a first-line thyroid-function test. *Lancet* 2001;357:1013-4.

SUMMARY

Background Measurement of serum thyrotropin (TSH) is widely regarded as the single best test of thyroid function, and if the result is normal the patient is considered to be euthyroid and no further tests are done. There are, however, patients with thyroid dysfunction in whom serum TSH concentrations are within the normal range. They include patients with central hypothyroidism, TSH-secreting pituitary tumors or thyroid hormone resistance. This study was done to determine how often an important diagnosis would be missed if thyroid function were evaluated only by measurement of serum TSH.

Methods Serum TSH and thyroxine (T₄) were measured in 56,000 samples during a one-year period in the laboratory of the Royal Liverpool University Hospital, Liverpool, United Kingdom, which serves a population of 471,000 people. The samples were obtained from patients in general practices in the area and patients in the hospital. These two tests were followed by measurements of serum free T₄, cortisol, estradiol or testosterone, gonadotropins, and prolactin if indicated.

Results Seventeen patients with possible central hypothyroidism were identified during the course of this study. Their serum TSH concentrations were within the normal reference range (0.17 to 3.2 mU/L), but they had low serum T₄ concentrations (1.3 to 5.3 µg/dL [17 to 68 nmol/L]) and

low serum free T₄ concentrations (<0.2 to 0.6 ng/dL [2.3 to 8.3 pmol/L]). A primary care physician had ordered the serum TSH measurement in 11 patients.

Fifteen of the patients proved to have hypopituitarism, of whom 9 had panhypopituitarism (including 6 who had undetectable serum cortisol concentrations (<1 µg/dL [27 nmol/L])). The other 2 patients had severe nonthyroidal illness. The 17 patients ranged in age from 29 to 84 years (median, 69); 9 were women and 8 were men. Many of the patients had nonspecific symptoms such as fatigue and lethargy, and none had been suspected to have hypopituitarism. The causes of hypopituitarism were a pituitary adenoma in 6 patients (1 prolactinoma, 5 non-secretory adenomas), the empty sella syndrome in 2 patients, and not known in 7 patients. During the same period, 11 patients (age range, 22 to 74 years; 4 women and 7 men) suspected to have hypopituitarism were referred to the hospital, and in all 11 the diagnosis was confirmed.

Overall, there were 20 cases of primary hypothyroidism for each case of central hypothyroidism. The estimated incidence of hypopituitarism, based on the total of 26 cases and the population base of 471,000, was 55 cases per million people per year.

Conclusion Both serum TSH and T₄ or free T₄ should be measured in patients in whom thyroid dysfunction is suspected.

COMMENTARY

The results of this study serve as a useful reminder that no single test will identify all patients with thyroid dysfunction, and also that some patients with hypopituitarism have very few symptoms. Important information, however, is missing. Were there any patients with low serum TSH and low serum T₄ concentrations, and if so how many had central hypothyroidism and how many had nonthyroidal illness? Were there any patients with high serum TSH concentrations and low serum T₄ concentrations who proved to have central hypothyroidism? How many patients with primary hypothyroidism were identified, and how many of them had overt hypothyroidism and how many had subclinical hypothyroidism?

Most patients with central hypothyroidism have normal serum TSH concentrations, but the concentrations may

be low or high. For example, in a study of 41 patients, 5 had low, 29 had normal, and 7 had high serum TSH concentrations (1). Loss of the night-time surge in TSH secretion, secretion of TSH with decreased biological activity, or both, account for the apparent anomaly of normal (or high) serum TSH concentrations and low thyroid hormone secretion.

The single-test approach to evaluating thyroid function, including whether that test should be measurement of serum TSH or free T₄, has been evaluated in several studies in which both were measured in all patients (2,3). The serum TSH first protocol misses fewer patients because it identifies patients with subclinical hypothyroidism and subclinical hyperthyroidism, but the patients it misses, for example those with central hypothyroidism, may be harmed more if missed. The solution is not to do both tests routinely, but to have a rather low threshold for measuring serum free T₄ in

patients with normal serum TSH concentrations.

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Urinary iodine excretion varies substantially from month to month in normal subjects

Andersen S, Pedersen KM, Pedersen IB, Laurberg P. Variations in urinary iodine excretion and thyroid function. A 1-year study in healthy men. *Eur J Endocrinol* 2001;144:461-5.

SUMMARY

Background Iodine intake varies substantially in different regions and within regions. Furthermore, in individual subjects, iodine intake can vary from day to day, and even within the day, depending on dietary intake, the iodine content of water consumed, and supplementary iodine intake, either as iodine alone or iodine as a constituent of vitamin and mineral supplements. This study was undertaken to determine the variation of urinary iodine excretion during the course of one year in normal subjects residing in an area of mild iodine deficiency.

Methods Urinary iodine excretion and serum thyrotropin (TSH) and thyroid hormones were measured in urine and blood samples collected between 9 a.m. and noon once monthly for 12 months in 15 normal men (median age, 38 years; range, 24 to 52). The men lived in the western part of Denmark, in an area in which urinary iodine excretion is approximately 40 to 80 µg/day, corresponding to an iodine intake of approximately 50 to 100 µg/day. None of the men was taking vitamin or mineral supplements, and they continued their usual diet and activities during the study. Urinary iodine was measured by the ceric-arsenite method and the hormones by radioimmunoassays. All the samples from each man were analyzed in the same assay at the end of the study.

Results The mean annual urinary iodine concentration in the 15 men ranged from 29 to 81 µg/L; the overall mean value was 57 µg/L. The urinary iodine concentration in the individual samples from the group as a whole ranged from 10 to 260 µg/L, and based on inspection of a figure the

concentration varied nearly that much in several individual men. The coefficient of variation of the mean values in the 15 men was 23.6 percent, and the coefficient of variation of the individual values was 57.3 percent. The variation in values was lower when the results were expressed as estimated 24-hour urinary iodine excretion, calculated from the measured urinary iodine and creatinine concentrations and a 24-hour creatinine value of 1.52 g.

Considering individual urine samples, 7 percent contained less than 25 µg/L, indicative of severe iodine deficiency, and 8 percent contained more than 100 µg/L, indicative of iodine sufficiency. However, no man had a mean annual concentration <25 µg/L or >100 µg/L. The urinary iodine concentration was about 15 percent higher in the spring and summer than in the fall and winter (data not shown).

There was little change in serum TSH and thyroid hormone concentrations during the year. There was an inverse relationship between urinary iodine excretion and serum TSH concentrations in 10 of the men. Their mean annual urinary iodine values were 50 µg/24 hours or less, indicating that this is the threshold for at least marginal iodine sufficiency.

Conclusion Urinary iodine excretion varies substantially from month to month among normal subjects.

COMMENTARY

These findings obviously raise the question of the reliability of single measurements of urinary iodine excretion for assessing iodine intake. The variation is probably not surprising, given the variations in iodine content of different foods; the use or non-use of iodized salt depending on where one eats; and the variations in iodine content of water (1). Indeed, there is even a small diurnal variation in urinary iodine excretion, with a nadir in the morning and a peak in the late evening (2).

Iodine deficiency is defined in various ways, nearly always based on measurements of iodine in randomly collect-

ed urine samples, as was done in this study. The values may then be extrapolated to 24-hour values, usually based on measurements of creatinine in the urine sample, but that introduces error because of variations in creatinine content. Obviously, performing measurements in large numbers of people minimizes some of these variations and provides valuable information for assessing iodine intake in particular regions or countries. Nonetheless, the fact that there is substantial intra-individual variation should be kept in mind when evaluating these measurements.

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Encephalopathy as a manifestation of Hashimoto s disease

Byrne OC, Zuberi SM, Madigan CA, King MD. Hashimoto s thyroiditis - a rare but treatable cause of encephalopathy in children. *Eur J Pediatr Neurol* 2000;4:279-82.

SUMMARY

Background Patients with many different clinical manifestations of central nervous system dysfunction and high serum concentrations of antithyroid microsomal, antithyroid peroxidase or antithyroglobulin antibodies have been diagnosed as having Hashimoto s encephalopathy. These clinical manifestations include seizures, movement disorders, disorientation, confusion, delirium, coma, dementia, changes in personality, changes in cognition and memory, psychosis, dysphasia, hemiplegia, and ataxia. Many patients seemed to respond to glucocorticoid therapy. Most patients have been adult women, but a few adolescents have been reported. This article describes two girls said to have Hashimoto s encephalopathy.

Case Reports Case 1 was a 14-year-old girl who presented with a five-day history of decreased ability to concentrate and lapses in memory, hemiplegia, aphasia, and a generalized tonic-clonic seizure. Extensive biochemical studies, including thyroid function studies, and brain imaging studies were normal. She was treated with acyclovir, cefotaxime, and dexamethasone, and improved. Five months later, she had a similar illness, including another seizure, and also myoclonus and coma. She was intubated and ventilated for a short period. Biochemical and brain imaging studies were again normal, except for a slightly high serum thyrotropin (TSH) concentration (10.1 mU/L) and high serum concentrations of antithyroid microsomal and antithyroid peroxidase antibodies (measured in different assays). Electroencephalography revealed diffuse slowing. The patient recov-

ered during treatment with 60 mg of prednisolone daily for 10 days and then decreasing doses for 15 weeks, and remained well except for some neuropsychological dysfunction for the next three months.

Case 2 was a 12-year-old girl who was found to have goitrous autoimmune thyroiditis (serum TSH 18.5 mU/L, serum thyroxine 4.8 µg/dL [62 nmol/L], serum antithyroid peroxidase antibodies 2312 U/L [normal, <35]) and was treated with thyroxine for three months. Approximately two months later she began to have headaches and emotional lability, and then had several episodes of loss of consciousness and a generalized tonic-clonic seizure. On admission she was poorly responsive and had dysphasia and a right hemiparesis. Brain imaging studies were normal, as was cerebrospinal fluid; electroencephalography revealed some hemispheric asymmetry and slow waves. Serum TSH and thyroxine concentrations were normal, and the serum antithyroid peroxidase antibody concentration was 7044 U/L. She was treated with prednisolone for three weeks, with clinical improvement and a fall in serum antithyroid peroxidase antibody concentration to <35 U/L. Four weeks later she had another seizure, followed by coma. Her serum antithyroid peroxidase concentration was 2841 U/L. She was treated with intravenous methylprednisolone and then decreasing doses oral prednisolone for the next five months, with improvement.

Conclusion Hashimoto s encephalopathy should be considered in patients with unexplained encephalopathy.

COMMENTARY

The description of the neurological symptoms and signs in these two girls lacks clarity, but in general their illnesses were similar to those described in adults said to have Hashimoto s encephalopathy, as listed in the background section. That brief listing does not adequately convey the variability of the clinical manifestations of this disorder, as described in the two largest series of cases, comprising 25 women and 2 men (1,2). Similarly, the course and outcome are variable. Some patients have progressive course and others a fluctuating one, with remissions and relapses. Some patients recover completely and others have persistent neurological, cognitive or behavioral dysfunction. There are no consistent neuroradiological abnormalities, and the electroencephalographic changes and cerebrospinal fluid changes,

most often an increased protein concentration, are nonspecific. What has led to this array of findings to being labeled Hashimoto s encephalopathy is that nearly all patients have had high serum concentrations of antithyroglobulin, antithyroid microsomal or antithyroid peroxidase antibodies. Nearly all have had normal thyroid function, at least when they had encephalopathy.

The diagnosis of Hashimoto s encephalopathy seems to be popular among some neurologists. However, attributing this array of symptoms and signs to Hashimoto s disease, on the basis of high serum antithyroid antibody concentrations, is unjustified. There is no evidence that any antithyroid antibodies react with any component of neural tissue. Many people, especially older women, have high serum antithyroid antibody concentrations and normal thyroid function, but this syndrome of encephalopathy seems to be rare.

Thus, the relationship is very likely to be a chance association. The improvement in neurological symptoms and signs in response to glucocorticoid therapy, which seems to be a uniform finding in these patients, is hardly evidence linking the encephalopathy to Hashimoto s disease.

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Thyroxine therapy improves immunological abnormalities but does not alter thyroid size in euthyroid patients with Hashimoto's disease

Padberg S, Heller K, Usadel KH, Schumm-Draeger P-M. One-year prophylactic treatment of euthyroid Hashimoto's thyroiditis patients with levothyroxine: is there a benefit? *Thyroid* 2001;11:249-55.

SUMMARY

Background Administration of thyroxine (T₄) to patients with Hashimoto's disease (goitrous autoimmune thyroiditis) who have hypothyroidism not only ameliorates the hypothyroidism but also may reduce goiter size and reverse some of the immunological abnormalities associated with the disease. This study was undertaken to determine the effects of T₄ therapy on serum antithyroid antibody concentrations and peripheral blood and intrathyroidal lymphocyte subsets in euthyroid patients with Hashimoto's disease.

Methods The main study subjects were 21 euthyroid patients (20 women and 1 man; age range, 37 to 51 years) with Hashimoto's disease, defined as normal serum thyrotropin (TSH), free T₄ and free triiodothyronine (T₃) concentrations, high serum antithyroid peroxidase (TPO) antibody concentrations, and appropriate thyroid cytology. None had thyroid enlargement. Alternate patients were treated with T₄ in a dose sufficient to reduce their serum TSH concentrations to 0.3 to 1.0 μU/mL (low-normal) for 1 year. Other study subjects were 10 patients with a non-toxic nodular goiter (5 women and 5 men; age range, 29 to 77 years) and 13 normal subjects (10 women and 3 men; age range, 24 to 58 years), none of whom had high serum anti-TPO antibody concentrations. Serum antithyroid antibodies and peripheral blood and thyroid lymphocyte subsets (T-helper cells [CD3/CD4], cytotoxic T cells [CD3/CD8], B cells [CD19], natural killer cells [CD56], activated T-helper cells [CD4/HLA-DR⁺], and activated T-cytotoxic cells [CD8/HLA-DR⁺] were measured before and after 1 year in the T₄-treated and untreated patients with Hashimoto's disease and at baseline in the other groups (excluding thyroid cells in the normal subjects).

Results There were no differences in the proportions of the types of lymphocytes in the peripheral blood of the four groups of subjects. The proportion of thyroidal T cells that were T helper cells was higher in the patients with Hashimoto's disease than those with a multinodular goiter.

The changes in serum TSH, free T₄, anti-TPO and anti-thyroglobulin antibody concentrations in the T₄-treated and untreated patients are shown in the table.

	Serum TSH (μU/mL)		Serum Free T ₄ (ng/dL)*		Serum Anti-TPO (U/mL)		Serum Anti-Tg (U/mL)	
	Before	After	Before	After	Before	After	Before	After
T ₄ treatment	2.9	0.7*	1.0	1.4*	759	520*	147	86
No treatment	2.0	2.4	1.2	1.2	1328	1680	262	315

To convert serum free T₄ values to nmol/L multiply by 12.9.
*P<0.05 compared with before treatment.

Thyroid volume did not change, and it was not correlated with serum anti-TPO concentrations at any time in either group. The proportion of thyroid lymphocytes that were B cells decreased during T₄ treatment from approximately 6 percent to 3 percent, but there was no change in the other lymphocyte subsets.

Conclusion Treatment with T₄ may slow the progression of Hashimoto's thyroiditis.

COMMENTARY

These patients had what might be called minimal autoimmune thyroiditis, as defined by high serum anti-TPO antibody concentrations and thyroid cytology. The decreases in serum antibody concentrations and the proportion in intrathyroidal T lymphocytes during the 1-year T₄-treatment period were small, and there was no change in thyroid size (although no actual data on thyroid volume are given). The greater than 75 percent fall in TSH secretion would be expected to cause some atrophy of thyroid follicular cells, and therefore the lack of change in thyroid size suggests that a substantial fraction of the volume of the thyroid probably consisted of

infiltrating lymphocytes.

Among euthyroid and hypothyroid patients with goitrous autoimmune thyroiditis, T₄ therapy often reduces serum antithyroid antibody concentrations and goiter size (1,2). In these patients, the decrease in goiter size is probably due to atrophy of hyperplastic thyroid follicular cells and a decrease in infiltrating lymphocytes. Possible explanations for the latter change include decreased expression of thyroid-cell antigens, due to decreased TSH secretion, and decreased stimulation of intrathyroidal lymphocytes, due to a decrease in T₄ and T₃ concentrations in the extracellular fluid within the thyroid gland.

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Increased thyroid hormone receptors in cardiac muscle of patients with heart failure

D'Amati G, di Gioia CRT, Mentuccia D, Pistilli D, Proietti-Pannunzi L, Miraldi F, Gallo P, Celi FS. Increased expression of thyroid hormone receptor isoforms in end-stage human congestive heart failure. *J Clin Endocrinol Metab* 2001;86:2080-4.

SUMMARY

Background Thyroid hormone has important chronotropic and inotropic actions on the heart, many of which are mediated by thyroid hormone nuclear receptors. Patients with cardiac failure may have low serum thyroid hormone concentrations, especially low serum triiodothyronine (T_3) concentrations, but whether thyroid hormone receptors are altered in the myocardium of patients with heart failure is not known.

Methods The expression of mRNAs for the $\alpha 1$, $\alpha 2$ and $\beta 1$ isoforms of the receptor was measured in myocardial tissue from 16 patients (3 women and 13 men; mean age, 58 years; mean ejection fraction, 54 percent) undergoing elective coronary artery bypass surgery and 14 patients with end-stage congestive heart failure who underwent heart transplantation. Among the latter group 8 patients (2 women and 6 men; mean age, 56 years; mean ejection fraction, 25 percent) had ischemic heart disease and 6 patients (3 women and 3 men; mean age, 44 years; mean ejection fraction, 22 percent) had dilated cardiomyopathy. All the patients had normal serum free thyroxine (T_4), free T_3 and thyrotropin (TSH) concentrations, and none was taking thyroid hormone, amiodarone, or propranolol or a related drug.

The mRNAs were measured by a competitive reverse transcriptase-polymerase chain reaction method using 100 ng of myocardial mRNA and RNA standards containing most of the sequences of the $\alpha 1$, $\alpha 2$ (which does not bind T_3), and $\beta 1$ isoforms of the receptor (the fourth isoform [$\beta 2$] is limited largely to neural tissue). In addition, the myocardial

content of these receptors was studied by immunostaining using an antibody against a region of the α receptor common to both the $\alpha 1$ and $\alpha 2$ isoforms and by Western blotting using an antibody against a region common to the $\alpha 1$ and $\beta 1$ isoforms and an antibody against the $\beta 1$ isoform alone.

Results The mean (\pm SE) content of mRNA in molecules/100 ng of total RNA for the $\alpha 1$ receptor isoform in the myocardium was 6400 in the control group, 65,625 in the ischemic heart disease group, and 158,333 in the dilated cardiomyopathy group ($P=0.008$). The respective values for the $\alpha 2$ isoform of the receptor were 2700, 30,000, and 30,000 molecules/100 ng total RNA, and the respective values for the $\beta 1$ isoform were 2800, 33,937, and 53,330 molecules/100 ng total RNA (both $P=0.008$).

The nuclei of cardiac myocytes for all three patient groups were intensely by the anti- $\alpha 1$ isoform antibody. The Western blotting studies revealed a single band corresponding to the molecular weight of the $\alpha 1$ isoform of the receptor in all three groups, but the bands were much more intense in the myocardial tissue from the patients with ischemic heart disease and dilated cardiomyopathy, as compared with the control group.

Conclusion The myocardial content of the $\alpha 1$, $\alpha 2$ and $\beta 1$ isoforms of thyroid hormone nuclear receptors, especially that of the $\alpha 1$ isoform, is increased in patients with end-stage congestive heart failure caused by ischemic heart disease or dilated cardiomyopathy.

COMMENTARY

It is tempting to think that the increase in thyroid hormone-nuclear receptor mRNA and protein in the myocardium of these patients with heart failure represents an attempt by the myocytes to compensate for a decrease in T_3 content, and thus maintain the inotropic action of T_3 in the myocardium. The larger increase in the $\alpha 1$ isoform, which is the dominant form in myocardial tissue and the form thought to mediate most of the cardiac actions of T_3 , further supports the physiological relevance of these findings. One problem with this notion is that the patients

with end-stage heart failure in this study did not have low serum free T_4 and T_3 concentrations, but myocardial concentrations of T_3 still could have been low as a result of decreased conversion of T_4 to T_3 within the myocytes.

These results add to the debate about the value of administration of T_4 or T_3 to patients with nonthyroidal illness in general and congestive heart failure in particular. With respect to the latter, there is evidence not only that patients with the lowest serum T_3 concentrations have the poorest prognosis (1), but also that administration of T_4 for 3 months has beneficial effects on cardiac function in patients

with cardiomyopathy (2).

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Lack of association between serum interleukin-6 and serum triiodothyronine in rheumatoid arthritis

Wellby ML, Kennedy JA, Pile K, True BS, Barreau P. Serum interleukin-6 and thyroid hormones in rheumatoid arthritis. *Metabolism* 2001;50:463-7.

SUMMARY

Background Many patients with nonthyroidal illness have abnormalities in thyroid function, most often low serum triiodothyronine (T_3) concentrations. The low concentrations are caused by decreased extrathyroidal conversion of thyroxine (T_4) to T_3 , which may be caused, at least in part, by increased serum concentrations of cytokines. Among the many cytokines, interleukin-6 has been most often implicated in decreased conversion of T_4 to T_3 . In this study the correlation between serum interleukin-6 and thyroid hormone concentrations was evaluated in patients with rheumatoid arthritis and other rheumatologic disorders.

Methods The study subjects were 16 patients (9 women and 7 men; mean age, 61 years) with untreated rheumatoid arthritis; 35 patients (23 women and 12 men; mean age, 64 years) with rheumatoid arthritis receiving therapy with nonsteroidal anti-inflammatory and disease-modifying drugs; 27 patients (14 women and 13 men; mean age, 63 years) with untreated non-inflammatory musculoskeletal disorders (osteoarthritis and regional pain syndromes); and 27 patients (21 women and 6 men; mean age, 66 years) with non-inflammatory musculoskeletal disorders receiving nonsteroidal anti-inflammatory drugs. Patients receiving glucocorticoids and other drugs that alter pituitary-thyroid function were excluded. Based on a dietary questionnaire the nutritional status of the groups was similar. Serum interleukin-6 (normal, <14.9 pg/mL), C-reactive protein (normal, <10 mg/L), free T_3 , and free T_4 were measured in all patients.

Results The mean serum interleukin-6 and C-reactive protein concentrations were statistically significantly higher in the patients with untreated rheumatoid arthritis than in the other three groups (table). The patients with treated rheumatoid arthritis also had higher serum interleukin-6 and C-reactive protein values than the two groups of patients with musculoskeletal disorders. The mean serum free T_3 concentrations were similar (and normal) in all four groups, as were the mean serum free T_4 and TSH concentrations. There were no significant correlations between serum interleukin-6 concentrations and serum free T_3 , free T_4 or TSH concentrations in any of the groups.

Table. Serum Interleukin-6, C-Reactive Protein, and Free T_3 Concentrations in Patients with Rheumatoid Arthritis and Non-inflammatory Musculoskeletal Disorders.

	Serum Interleukin-6 (pg/mL)	Serum C-Reactive Protein (mg/L)	Serum Free T_3 (ng/dL [\pm SE])*
Rheumatoid arthritis			
Untreated (n=16)	37.5	41.3	0.23 \pm 0.01
Treated (n=35)	9.9	13.3	0.20 \pm 0.01
Musculoskeletal disorders			
Untreated (n=27)	2.5	5.8	0.24 \pm 0.01
Treated (n=27)	6.6	8.1	0.22 \pm 0.01

*To convert serum free T_3 values to pmol/L multiply by 0.0154.

Conclusion Patients with rheumatoid arthritis have high serum interleukin-6 concentrations, but the high values are not associated with any abnormalities in thyroid function.

COMMENTARY

This study provides evidence against a role for interleukin-6 in the changes in thyroid function that occur in patients with nonthyroidal illness. However, the patients with untreated rheumatoid arthritis were all outpatients, and were poorly characterized in terms of their level of symptoms, duration of symptoms, or degree of disability. Furthermore, despite having higher mean serum interleukin-6 concentrations than the patients in the other groups, some of the patients had normal values (based on inspection of a histogram).

In studies in which changes in thyroid function in patients with nonthyroidal illness, in particular low serum T_3 concentrations, were related to

interleukin-6, either the patients were more seriously ill and had higher serum interleukin-6 concentrations (1,2) or were normal subjects who received high-dose infusions of interleukin-6 (3). Even in these latter studies, however, the correlation between serum interleukin-6 concentrations and any changes in serum thyroid hormone concentrations was small. In sum, it is surely an oversimplification to attribute low serum T_3 concentrations or any of the other changes in thyroid function that occur in patients with nonthyroidal illness to any single substance or event.

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Correction

Presence of PAX8-PPAR γ 1 Gene Translocation Distinguishes Follicular Carcinoma from Other Follicular Lesions (March 2001:13). The abbreviation PPAR γ 1 stands for peroxisome proliferator-activated receptor, not peroxisome proliferator-activator as stated in the Background section of the Summary.