CLINICAL THYROIDOLOGY

VOLUME XIII • ISSUE 3 NOVEMBER 2001

A publication of the American Thyroid Association

CLINICAL THYROIDOLOGY

VOLUME XIII • ISSUE 3 NOVEMBER 2001

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

Designed By
Saratoga Graphics
7 Kaatskill Way
Ballston Spa, NY 12020
Telephone: (518) 583-0243
Kandra L. Files, Art Director
Email: kanlynn@sprynet.com

Clinical Thyroidology

Writing Commentaries for *Clinical Thyroidology*

Writing commentaries for *Clinical Thyroidology* can be a challenge, for several reasons. The physiology or pathophysiology underlying a study or the results of the study may need explanation or interpretation. The strengths or weaknesses of the study may need to be mentioned. The results of related studies often need to be described. Recommendations for action or inaction may be warranted. Sometimes, it is just more interesting to speculate on what the results of a study mean. On the other hand, space is always limited, because I think that more space should be devoted to the summary than the commentary, and the combination should be no longer than a page. In writing the commentary I often must therefore choose among the several topics listed above. I hope the commentaries are useful, but readers should focus on the summary, which I hope is an accurate description of the study. The new information is there, not in the commentary.

Robert D. Utiger, M.D.

Upcoming ATA Events

Future Meetings

74th Annual Meeting
October 9 to 13, 2002
Regal Biltmore Hotel
Los Angeles, CA

75th Annual Meeting
September 16 to 21, 2003
The Breakers
Palm Beach, FL

76th Annual Meeting
September 29 to October 3, 2004
Westin Bayshore Resort and Marina
Vancouver, British Columbia, Canada

13th International Thyroid Congress
October 30 to November 4, 2005
Buenos Aires, Argentina

Research Animals Available

Dutch goats with a mutation in the gene for thyroglobulin are available to interested investigators for research purposes. Homozygous affected goats have goiter and hypothyroidism; the severity of the changes depends on iodine intake. For further information contact: Professor J.J.M. de Vijlder, M.Sc., Ph.D. Laboratory of Pediatric Endocrinology, Emma Children's Hospital, Amsterdam, the Netherlands (j.j.devijlder@amc.uva.nl).

The characteristics of these goats are described in more detail in: Veenboer GJ, de Vijlder JJ. Molecular basis of the thyroglobulin synthesis defect in Dutch goats. Endocrinology 2991;132:377-81.

Visit the ATA on the web at: www.thyroid.org

Stressful life events precede the onset of hyperthyroidism caused by Graves disease but not by multinodular goiter

Matos-Santos A, Lacerda Nobre E, Costa JGE, Nogueira PJ, Macedo A, Galvao-Teles A, Jacome de Castro J. Relationship between the number and impact of stressful life events and the onset of Graves disease and toxic nodular goitre. Clin Endocrinol 2001;55:15-9.

SUMMARY

Background The possibility that stressful life events may provoke Graves disease, in particular Graves hyperthyroidism, was raised long ago, but strong supporting evidence is lacking. In this study the occurrence of such events during two time periods before the onset of symptoms of hyperthyroidism was determined in patients with Graves hyperthyroidism, patients with toxic nodular goiter, and control subjects.

Methods The study subjects were 31 patients with Graves hyperthyroidism, 31 patients with toxic nodular goiter, and 31 control subjects (recruited from among people attending a preventive medicine clinic). There were 22 women and 9 men in each group; their mean (±SD) ages were 38±11, 48±11, and 41±12 years, respectively. The diagnoses of Graves hyperthyroidism and toxic nodular goiter were based on standard clinical criteria. The patients with Graves hyperthyroidism and toxic nodular goiter constituted 76 percent and 82 percent, respectively, of the patients with these disorders seen at the investigators clinic during the study period.

Three months after recruitment, when all the patients were euthyroid, the study subjects were asked if they had undergone any of 47 stressful life events, such as death of a close family member or a major change in employment or living conditions, derived from the Life Experiences Survey, during the year before the onset of symptoms (divided into two periods, 0 to 6 months and 7 to 12 months). They also were asked to rate the events as being positive or negative on a 7-point scale (+3, extremely positive: -3, extremely negative). The questioner was not aware of the diagnosis.

Results The patients with Graves hyperthyroidism reported 173 events, as compared with 79 events in the patients with toxic nodular goiter and 50 events in the control subjects, mostly during the 7- to 12-month interval preceding the onset of hyperthyroidism (table).

Table. Time of Occurrence of Stressful Life Events in Patients with Hyperthyroidism and Control Subjects.

	Graves Hyperthyroidism (n=31)		Toxic Multinodular Goiter (n=31)		Control (n=31)	
	0-6 Months	7-12 Months	0-6 Months	7-12 Months	0-6 Months	7-12 Months
Positive events	4	23	3	7	5	13
Negative events	35	105	19	46	4	23
Neutral events	2	4	2	2	2	3
Total	41	132	24	55	11	39

In the patients with Graves hyperthyroidism, both the total number of negative events and their impact were significantly higher ($P<0.001$) than in the other two groups, and the total number of positive events and their impact was higher than in the patients with toxic nodular goiter ($P=0.004$).

Conclusion Stressful life events are more common before the onset of hyperthyroidism in patients with Graves disease than in patients with toxic nodular goiter or control subjects.

COMMENTARY

There are more case-control studies supporting than denying the hypothesis that some stressful life event initiates Graves hyperthyroidism. However, all the studies have the same limitations, including the willingness of patients to participate in the study (recruitment bias), the likelihood that more patients than control subjects recall stressful events (recall bias), difficulty in dating the onset of symptoms of hyperthyroidism, the possibility that the psychological effects of hyperthyroidism caused the stressful life events, and the fact that the patients and control subjects usually are asked to recall life events at different intervals in the past.

The strengths of this study were the inclusion of patients with toxic nodular goiter and the division of the year before the onset of hyperthyroidism into two 6-month periods. In this regard the finding that the patients with Graves hyperthyroidism had more stressful events during the 7- to 12-month period than the 0- to 6-month period before the onset of symptoms lends credence to the hypothesis. However, the paper itself has important limitations, including the lack of information about how far in the past the first symptoms of hyperthyroidism occurred (surely an important determinant of what is remembered), the number of subjects in each group who had positive or negative events, and what those events were.

The stress-Graves hyperthyroidism hypothesis has also been the subject of studies of the frequency of hyperthyroidism during periods of peace and civil strife in Northern Ireland (no difference) and Serbia (an increase during civil strife). These studies have their own limitations, notably ascertainment bias and varying criteria for diagnosis.

Suffice it to say that the association between stressful life events and Graves hyperthyroidism is unproven, nor is there a plausible biological explanation linking stressful events with activation of the disease.

Robert D. Utiger, M.D.

Methimazole pretreatment does not reduce the efficacy of radioiodine in patients with hyperthyroidism caused by Graves disease

Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves hyperthyroidism: one-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab 2001; 86:3488-93.

SUMMARY

Background Some patients with hyperthyroidism who are to be treated with radioiodine (I-131) are pretreated with an antithyroid drug. However, this pretreatment may reduce the efficacy of I-131. This prospective study was undertaken to determine the effect of pretreatment with methimazole on the efficacy of I-131 therapy in patients with hyperthyroidism caused by Graves disease.

Methods The study subjects were 61 patients with typical Graves hyperthyroidism (55 women and 6 men; mean age, 36 years). Patients with a large goiter, moderate or severe ophthalmopathy, or severe cardiac disease were excluded. The patients were randomly assigned to receive I-131 or 30 mg of methimazole daily until euthyroid and then, after a hiatus of 4 days, I-131. The dose of I-131 was 200 mCi (7.4 MBq)/g, based on measurements of thyroid volume by ultrasonography and 24-hour thyroid I-131 uptake immediately before treatment. The patients were then evaluated monthly for 1 year. Successful therapy was defined as euthyroidism or permanent hypothyroidism, based on two consecutive monthly measurements of serum free thyroxine (T_4). Treatment failure (persistent hyperthyroidism) was defined as a need for a second dose of I-131 or high serum free T_4 concentrations 1 year after administration of I-131.

Results The baseline demographic and clinical characteristics of the patients and the doses of I-131 in the methimazole-pretreatment group and the no-pretreatment group were similar. The median time to euthyroidism in the methimazole-pretreatment group was 12 weeks (range, 2 to 48).

The proportion of patients who were euthyroid or hypothyroid 3, 6 and 12 months after I-131 treatment was similar in the two groups (table).

Table. Effects of Treatment in the Methimazole-Pretreatment and the No-Pretreatment Groups.*

	Proportion of Patients Who Were Euthyroid or Hypothyroid		
	3 Months	6 Months	12 Months
Pretreatment with methimazole	56%	86%	86%
No pretreatment	58%	84%	84%

*Results extrapolated from figure 1 in Andrade et al.

At 1 year, 16 patients in the methimazole-pretreatment group (55 percent) had hypothyroidism, 9 (31 percent) were euthyroid, and 4 (14 percent) had persistent hyperthyroidism, as compared with 18 (56 percent), 9 (28 percent), and 5 (16 percent), respectively, in the no-pretreatment group.

Conclusion In patients with Graves hyperthyroidism the efficacy of I-131 therapy is not reduced by pretreatment with methimazole.

COMMENTARY

With few exceptions, patients with hyperthyroidism for whom treatment with I-131 is planned should not be pretreated with an antithyroid drug before I-131 is administered. For one thing, the speed of onset of action of the two types of treatment does not differ very much. For another, why expose patients to the side effects of an antithyroid drug if prolonged treatment intended to allow remission is not intended? One exception is patients with severe hyperthyroidism, because antithyroid drug therapy does reduce thyroid secretion slightly more rapidly than does I-131 therapy, and drug therapy is likely to minimize the risk of a clinically important exacerbation of hyperthyroidism after the administration of I-131. Another exception is patients in whom I-131 administration must be delayed, for example, because the patient recently received a high dose of iodine, usually in the form of a radiographic contrast agent.

Based on the results of this prospective study and several retrospective studies (1,2), pretreatment with methimazole for weeks or months does not reduce the efficacy of I-131 therapy. In contrast, pretreatment with propylthiouracil does seem to decrease the efficacy of I-131, although it has not been studied so carefully (2,3).

Unplanned pretreatment also occurs - as when patients with Graves hyperthyroidism who initially chose antithyroid drug therapy have side effects of the drug or do not have a remission of Graves disease during prolonged drug therapy and therefore need to be treated with I-131. The results of this study should apply to these patients if they were treated with methimazole. For now at least, patients who received prolonged propylthiouracil therapy should receive a higher dose of I-131 than would ordinarily be given (3). Whichever drug they received, it is likely that the longer the interval between cessation of the drug and I-131 administration the better, but in fact the optimal time interval is not known.

Administration of an antithyroid drug after administration of I-131 may reduce the efficacy of I-131, but that is a separate topic.

Robert D. Utiger, M.D.

References

1. Marcocci C, Gianchecchi D, Masini I, et al. A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves hyperthyroidism. J Endocrinol Invest 1990;13:513-20.

2. Imesis RE, Van Middlesworth L, Massie JD, et al. Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab 1998;83:685-7.

3. Hancock LD, Tuttle RM, LeMar H, et al. The effect of propylthiouracil on subsequent radioactive iodine therapy in Graves disease. Clin Endocrinol 1997; 47:425-30.

Long-acting octreotide is an effective therapy for patients with thyrotropin-secreting pituitary adenomas

Caron P, Arlot S, Bauters C, Chanson P, Kuhn J-M, Pugeat M, Marechaud R, Teutsch C, Vidal E, Sassano P. Efficacy of the long-acting octreotide formulation (octreotide-Lar) in patients with thyrotropin-secreting pituitary adenomas. J Clin Endocrinol Metab 2001;86:2849-53.

SUMMARY

Background Central hyperthyroidism is characterized by hyperthyroidism, a diffuse goiter, and normal or high serum thyrotropin (TSH) concentrations, and is nearly always caused by a TSH-secreting pituitary micro- or macroadenoma. The usual treatment is transsphenoidal resection of the tumor, but that is not uniformly successful. The somatostatin analog octreotide effectively reduces TSH secretion in most patients, but must be given subcutaneously several times daily or by continuous subcutaneous infusion. This study was undertaken to determine the efficacy of a long-acting formulation of octreotide in patients with TSH-secreting adenomas.

Methods The study subjects were 11 patients (6 women and 5 men; mean [±SE] age, 43±3 years) with a TSH-secreting pituitary adenoma. Nine patients had macroadenomas and 2 had microadenomas. Three patients had been treated with transsphenoidal surgery, 1 with radiation, and 3 with both surgery and radiation; all had subsequently received octreotide for 4 to 72 months with normalization of their serum free thyroxine (T_4) and triiodothyronine (T_3) concentrations. This treatment was then withdrawn for 34±6 days, at which time the patients were clinically hyperthyroid and their serum TSH, free T_4, and free T_3 concentrations had increased to values similar to those before octreotide was initiated. They were then treated with long-acting octreotide (octreotide-Lar), 20 mg intramuscularly once a month for 6 months, with clinical and biochemical studies at 3 and 6 months, 30 days after the last injection.

Results During octreotide-Lar treatment, all patients improved clinically and their mean serum TSH, free T_4, and free T_3 concentrations decreased significantly (table). At base line, 3 patients had high and 8 had normal serum TSH concentrations, and 8 patients had high and 3 patients had high normal serum free T_4 concentrations (presumably as a result of previous treatment). During treatment, serum TSH concentrations were normal in all patients, and serum free T_4 and free T_3 concentrations were normal in all but 1 patient. In this patient the dose of octreotide-Lar was increased to 30 mg monthly after 3 months, but the serum free T_4 concentration remained high. The responses were similar in patients who had surgery or radiation therapy and those who had not, and the responses during octreotide-Lar treatment were similar to the responses during previous octreotide treatment. Follow-up imaging studies were not done.

Table. Mean (±SE) Serum TSH, Free T_4 and Free T_3 Concentrations during Octreotide-Lar Therapy in 11 Patients with a TSH-Secreting Adenoma.

	Base Line	3 Months	6 Months	Normal Values
Serum TSH (mU/L)	2.8±0.4	1.6±0.3*	1.4±0.2*	0.3-5.5
Serum free T_4 (ng/dL)	2.3±0.3	1.2±0.1*	1.3±0.1*	0.7-1.9
Serum free T_3 (ng/dL)	0.5±0.1	0.3±0.03*	0.3±0.02*	0.2-0.4

*P≤0.05, as compared with base line.
To convert serum free T_4 and free T_3 values to pmol/L, multiply by 12.9 and by 0.0154, respectively.

The adverse effects of treatment were minor digestive symptoms and pain at injection sites for several days after the injections. No patient had changes in the results of gall bladder ultrasonography during treatment.

Conclusion Octreotide-Lar is an effective and safe treatment for patients with TSH-secreting pituitary adenomas.

COMMENTARY

Surgical treatment of patients with TSH-secreting pituitary adenomas is often unsuccessful; among 120 patients 33 percent were deemed cured, 33 percent improved, and 34 percent unchanged (1). Treatment with octreotide has proven to be more effective in reducing serum TSH and thyroid hormone concentrations, and it often also decreases tumor size, but must be given very often (1). Long-acting preparations of octreotide such as octreotide-Lar, given once monthly as in this study, and lanreotide (2), which is given every two weeks, seem to be as effective as octreotide. Lanreotide acts in hours, like octreotide (2). The speed of onset of action of octreotide-Lar is not known, but rapid onset of action is not a very important consideration in patients who will be treated for a prolonged period. Given their efficacy, these long-acting drugs should probably supplant surgery as the treatment of choice for most patients with these tumors. Treatment might not have to be life long, because the adenomas might disappear, like some prolactinomas do with prolonged dopamine agonist drug treatment.

Robert D. Utiger, M.D.

References

1. Beck-Peccoz P, Brucker-Davis F, Persani L, et al. Thyrotropin-secreting pituitary tumors. Endocr Rev 1996;17: 610-38.

2. Kuhn JM, Arlot S, Lefebvre H, et al. Evaluation of the treatment of thyrotropin-secreting pituitary adenomas with a slow release formulation of the somatostatin analog lanreotide. J Clin Endocrinol Metab 2000;85:1487-91.

Preexisting obesity, weight loss before treatment, and hypothyroidism after treatment are associated for excess weight gain during and after treatment in patients with hyperthyroidism

Dale J, Daykin J, Holder R, Sheppard MC, Franklyn JA. Weight gain following treatment of hyperthyroidism. Clin Endocrinol 2001;55:233-9.

SUMMARY

Background Many, but not all, patients with hyperthyroidism lose weight during the course of their illness. Whether weight was lost or not, excess weight gain during treatment is a common complaint. This study was undertaken to determine the extent of weight gain during treatment and the factors that determine the amount gained.

Methods The study subjects were 162 patients with hyperthyroidism (138 women, 24 men; median age, 40 years; range, 18 to 88) who were followed for at least 6 months after the initiation of therapy. Among them, 95 (59 percent) had Graves hyperthyroidism, 37 (23 percent) had a toxic multinodular goiter, and 30 (18 percent) had another cause of hyperthyroidism. Treatment consisted of an antithyroid drug for 18 months in 87 patients (54 percent), an antithyroid drug for <4 months and then radioiodine in 62 patients (38 percent), and thyroidectomy in 13 patients (8 percent). Height was measured once at base line, and body weight and thyroid function were measured at base line and during follow-up (median, 18 months; range, 6 to 122). During or after treatment, 31 patients (19 percent) developed hypothyroidism and were treated with thyroxine (T_4), 29 (18 percent) had transient hypothyroidism, and 102 (63 percent) never had hypothyroidism.

Results At the time of diagnosis, 95 patients (59 percent) reported having lost weight, 58 (36 percent) reported no change in weight, and 9 (5 percent) reported weight gain; 62 (38 percent) were overweight (body mass index [BMI] >25 kg/m^2) and 16 (10 percent) were obese (BMI >30 kg/m^2). At that time, the patients' mean (±SE) weight and BMI were 65.8±1.1 kg and 24.4±0.4 kg/m^2, respectively. Their final weight was 71.2 kg, an increase of 5.4 kg (8 percent), and their final BMI was 26.4 kg/m^2, an increase of 2.0 kg/m^2 (8 percent); 30 (18 percent) were obese at the last examination. Weight gain during follow-up averaged 3.7 kg/year.

Weight gain during follow-up was associated with younger age, Graves disease as the cause of hyperthyroidism, weight loss before diagnosis, hypothyroidism requiring T_4 therapy, and longer duration of follow-up (P≤0.05). For example, patients aged ≤30 years gained 7.5 kg, as compared with 4.6 kg among those aged >70 years; patients who lost weight while hyperthyroid gained 6.7 kg, as compared with 2.4 kg among those who gained weight then; and those with hypothyroidism requiring T_4 therapy gained 8.1 kg, as compared with 4.6 kg among those who never had hypothyroidism. The 162 patients who were followed for 6 months gained 2.1 kg, the 79 patients followed for 48 months gained 5.5 kg, and the 27 patients followed for 48 months gained 9.9 kg (P=0.002).

The independent factors that predicted weight gain were BMI>25 kg/m^2 and more weight loss before treatment, Graves' disease (perhaps a surrogate for younger age), hypothyroidism requiring T_4 therapy, and duration of follow-up (P≤0.05). Factors not associated with weight gain were sex and radioiodine therapy (vs. antithyroid drug therapy).

Conclusion In patients with hyperthyroidism, excess weight gain during and after treatment is most likely to occur in patients who were obese before the onset of hyperthyroidism, those who lost more weight before diagnosis, and those who become hypothyroid after treatment.

COMMENTARY

Nearly all patients with hyperthyroidism gain weight when treated, whether they had lost weight or not. The finding of greater weight gain in younger patients suggests that a higher percentage of them had lost weight, a finding at odds with other studies (1). It seems physiologically appropriate that patients with hyperthyroidism who have lost the most weight gain the most weight with treatment, and it is physiologically understandable that those who become hypothyroid gain more weight than those who do not. The most easily modifiable, or rather preventable, factor associated with excess weight gain is hypothyroidism. In this study hypothyroidism was not linked to radioiodine therapy, but in another study patients treated with an antithyroid drug for 18 months gained less weight than those who were treated with radioiodine or surgery and then became hypothyroid and received T_4 (2). As a practical matter, some patients do not comply with antithyroid drug therapy or do not accept a recommendation for radioiodine therapy because of fear of weight gain.

The fact that patients with hyperthyroidism gain, have no change, or lose weight suggests that it can stimulate appetite independent of its metabolic actions on peripheral tissues. What is more, in some patients the stimulation may persist indefinitely despite normal metabolic activity. Why appetite should be affected so variably is a mystery.

Robert D. Utiger, M.D.

References

1. Nordyke RA, Gilbert, FI Jr, Harada ASM. Graves disease. Influence of age on clinical findings. Arch Intern Med 1988;148:626-31.

2. Tigas S, Idiculla J, Beckett G, et al. Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? Thyroid 2001;10:1107-11.

Mortality is transiently increased after diagnosis in patients with subclinical hyperthyroidism

Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet 2001;358:861-5.

SUMMARY

Background Subclinical hyperthyroidism is characterized by low serum thyrotropin (TSH) and normal serum thyroxine (T_4) and triiodothyronine (T_3) concentrations, with or without symptoms and signs of hyperthyroidism. The long-term consequences of subclinical hyperthyroidism include an increased risk of cardiac dysfunction, osteoporosis, and overt hyperthyroidism. This population-based study was undertaken to determine the effects of subclinical hyperthyroidism on mortality.

Methods The study group was 1191 subjects (681 women, and 510 men) aged 60 years or older (mean age, 70) registered at one primary care practice in Birmingham, United Kingdom in 1988-89. Patients known to have thyroid disease were excluded. At base line, serum TSH was measured using an assay with a sensitivity of 0.1 mU/L. Patients with abnormal serum TSH values were examined and serum free T_4 and free T_3 were measured. Those with abnormal serum TSH values alone were reevaluated yearly. The patients were subdivided into groups with low (<0.5 mU/L), normal (0.5 to 5.0 mU/L), and high (>5.0 mU/L) serum TSH concentrations. In 1999, the status of the patients was determined from the records of the practice or the National Health Service Central Register, and the causes of death were ascertained from death certificates for the 509 patients (242 women and 267 men) who had died. The causes of death among these 509 patients were compared with age-, sex-, and year-specific mortality data for the whole of England and Wales. The mean duration of follow-up was 8.2 years.

Results At base line, 71 patients (6 percent) had low serum TSH concentrations, of whom 25 (35 percent) had a goiter and 1 had overt hyperthyroidism. There were 94 patients (8 percent) with high serum TSH concentrations, of whom 18 (19 percent) had overt hypothyroidism. Subsequently, 3 patients with subclinical hyperthyroidism had overt hyperthyroidism, and 30 patients with subclinical hypothyroidism had overt hypothyroidism.

During follow-up, 34 of the 70 patients with subclinical hyperthyroidism (48 percent) died, as compared with 31 of the 76 patients with subclinical hypothyroidism (41 percent) and 444 of the remaining 1045 patients (42 percent). The overall death rate was very similar to the expected rate, based on the country-wide data. There were, however, greater than expected numbers of deaths from any cause and from circulatory disorders among the patients with subclinical hyperthyroidism at 2, 3, 4, and 5 years of follow-up (data for 2 and 4 years shown in the table). Among the patients with normal or high serum TSH concentrations, the all-cause and circulatory-disorder death rates were similar to the expected rates at all times.

Table. Numbers of Deaths and Standardized Mortality Ratios in Patients with Subclinical Hyperthyroidism at Base Line.

	No. of Deaths, SMR*, 1 Year	No. of Deaths, SMR, 2 Years	No. of Deaths, SMR, 4 Years	No. of Deaths, SMR, End of Follow-up
All causes				
Serum TSH	1	14	21	17
<0.5 mU/L	0.2 (0.0-2.1)	2.1 (1.2-3.5)	1.7 (1.1-2.7)	1.2 (0.9-1.7)
Circulatory disorders				
Serum TSH	0	7	11	17
<0.5 mU/L		2.1 (1.0-4.5)	1.9 (1.0-3.4)	1.3 (0.8-2.0)

*SMR, standardized mortality rate (95 percent confidence interval).

Conclusion In patients with subclinical hyperthyroidism, death rates from all causes and circulatory disorders are slightly higher than expected for several years after diagnosis.

COMMENTARY

These results add to the increasing evidence that subclinical hyperthyroidism is harmful. However, as in this study, the categorization of patients as having subclinical hyperthyroidism has often been based on single measurements, and the numbers of patients in the cohorts who had low serum TSH concentrations were small. Furthermore, it is important to remember that some patients, even ambulatory patients, who have nonthyroidal illnesses or are taking drugs to treat these illnesses have similar biochemical findings, and it may be that illness that causes both the patient s low serum TSH concentration and death. In this regard, there is no clinical information about the patients or adjustments for comorbidity in this study. However, the finding of no differences in death rates at 1 year argues against the possibility that the low serum TSH values were caused by soon-to-be fatal nonthyroidal illnesses.

The distinction between subclinical hyperthyroidism and nonthyroidal illness as a cause of low serum TSH concentrations is not an academic one. The former is due to an increase, however small, in thyroid hormone secretion or release, whereas it is, if anything, decreased in the latter. Furthermore, the increase may be transient, caused by thyroid inflammation. Therefore, intervention must be based on the absence of nonthyroidal illness, documentation of persistently low serum TSH concentrations, and some other evidence of thyroid hormone excess.

Robert D. Utiger, M.D.

Orbital radiotherapy is not beneficial in Graves ophthalmopathy

Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL, Earle JD, Forbes GS, Kline RW, Bergstrahl EJ, Offord KP, Rademacher DM, Stanley NM, Bartley GB. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves ophthalmopathy. Ophthalmology 2001;108:1523-34.

SUMMARY

Background Orbital radiotherapy is considered by many to be an established treatment for ophthalmopathy in patients with Graves disease, but the variable course of the ophthalmopathy has made documentation of the efficacy of this therapy difficult. This study was undertaken to evaluate the efficacy of radiotherapy by treating one eye and then 6 months later treating the other eye in a group of patients with Graves ophthalmopathy, which allowed evaluation of the effects of treatment versus no treatment in each patient for the initial 6-month interval.

Methods The study subjects were 42 patients (36 women, 6 men; median age, 48 years; range, 38 to 77) with mild to moderate Graves ophthalmopathy, as defined by eye pain, lacrimation, photophobia, or blurring of vision, and at least three of the following: conjunctival or eyelid edema; lid retraction; staring or bulging eyes; proptosis of ≥20 mm; and decreased eye movement. All patients had enlargement of the extraocular muscles on computed tomography of the orbits. The duration of ophthalmopathy ranged from 0.2 to 16 years (median, 1.3 years). Patients who had optic neuropathy and those who had received glucocorticoid therapy within the preceding two weeks were excluded; 19 patients had received glucocorticoid therapy earlier. Most patients had a history of hyperthyroidism, but all were euthyroid at base line. All had high serum concentrations of thyroid-stimulating immunoglobulins at that time and throughout the study. Twenty-one patients were smokers.

The patients were assigned to receive external radiation in a dose of 20 Gy delivered in 10 fractions to one randomly selected eye and sham radiation to the other eye. The radiation was directed in such a way that the opposite eye received a maximum dose of 2 Gy. The sham treatment was carried out in the same way, except that the radiation beam was blocked at its source. Six months later, the process was reversed. The patients were evaluated at base line and at 3, 6, 9, and 12 months by clinical examination; measurements of the volume of extraocular muscles and retroorbital fat and proptosis by computed tomography; and measurements of visual fields, muscle range of motion, visual acuity, and color vision by examiners who were unaware of the sequence of radiation. Two patients did not complete the study.

Results There were no differences in the volume of extraocular muscle and retroorbital fat, proptosis, muscle range of motion, the width of the lid fissure, or the other measurements between the untreated and treated eyes at 3 and 6 months. For example, the volume of muscle and fat decreased from 22.8 ml at base line to 22.7 ml at 6 months in the untreated eyes and from 23.3 ml to 23.0 ml in the treated eyes; the respective values for proptosis were 21.3 mm and 21.3 mm in the untreated eyes and 21.8 mm and 21.7 mm in the treated eyes. Subgroup analyses based on the duration of ophthalmopathy (≤1.3 years vs. >1.3 years), previous glucocorticoid therapy (vs. no therapy), smoking status, or degree of clinical activity of ophthalmopathy similarly revealed no differences in responses. None of six examiners was able to identify the treated eye by reviewing photographs taken at base line and at 6 months at a greater-than-chance rate.

At 12 months, the volume of muscle and fat in the eyes treated first and second was 22.9 ml, and proptosis was 21.3 mm in the eyes treated first and 21.4 mm in the eyes treated second. In addition, there were no differences in any of the other measurements at this time.

Conclusion Orbital radiotherapy is not effective in patients with Graves ophthalmopathy.

COMMENTARY

The standard treatments for patients with Graves ophthalmopathy are high oral or intravenous doses of a glucocorticoid, orbital radiotherapy, or surgical decompression of the orbits. Many patients have mild ophthalmopathy, and do not need any of these treatments. A few have more severe ophthalmopathy, and are thought to need more aggressive treatment. However, there are no widely accepted methods to guide selection of these treatments, and assessment of their efficacy is difficult, because objective assessment of ophthamopathy is difficult, and the disorder tends to subside in patients who are not treated (1).

Among the three treatments, orbital radiation has perhaps been the best studied, and the more objective studies have provided little evidence of benefit. Now comes this negative trial, unique in that patients served as their own control for the first 6 months. The authors can be faulted for not providing more information about the patients subjective responses to treatment, but they argue persuasively that it would be difficult to claim benefit for a treatment that does not alter the fundamental causes of the clinical manifestations of Graves opthalmopathy, which are enlargement of the extraocular muscles and retroorbital fat and impairment of muscle function. What is left is glucocorticoid therapy for patients with predominantly inflammatory ophthalmopathy and orbital decompression for those whose vision is threatened or already impaired.

Robert D. Utiger, M.D.

References

1. Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated ophthalmopathy. Clin Endocrinol 1995; 42:45-50.

Onset of symptomatic adrenal insufficiency during treatment of hypothyroidism

Murray JS, Jayarajasingh R, Perros P. Deterioration of symptoms after start of thyroid hormone replacement. BMJ 2001;323:332-3.

SUMMARY

Background Some patients with hypothyroidism caused by chronic autoimmune thyroiditis have concurrent autoimmune adrenal insufficiency. However, the clinical manifestations of the adrenal insufficiency may be obscured by the manifestations of hypothyroidism and become evident only after initiation of thyroxine (T_4) therapy. The possibility of adrenal insufficiency should be considered in patients with hypothyroidism whose symptoms do not improve or worsen or in whom new symptoms develop when they are treated with T_4, as exemplified by the two patients described here.

Case Reports

Patient 1 A 26-year-old woman with type 1 diabetes mellitus presented with a 5-week history of lethargy, nausea, postural lightheadedness, and episodes of hypoglycemia. The latter occurred despite a lack of change in food intake, physical activity, or dose of insulin. Her serum thyrotropin (TSH) concentration was high (37 mU/L) and her serum free T_4 concentration was low (1.0 ng/dL [12.7 pmol/L]). The patient was treated with 0.025 mg of T_4 daily, which was followed in a few days by worsening of her symptoms. Physical examination then revealed orthostatic hypotension and hyperpigmentation. Biochemical studies revealed hyponatremia (121 mmol/L), hyperkalemia (5.5 mmol/L), a low serum cortisol concentration (<0.7 µg/dL [20 nmol/L]) and a high plasma corticotropin (ACTH) concentration (1490 pg/mL [328 pmol/L], normal, <47 [10]). Plasma renin activity was high and plasma aldosterone concentration was low. Tests for antithyroid microsomal and antiadrenal antibodies were positive. The patient improved promptly in response to glucocorticoid and mineralocorticoid therapy. Four weeks later, her serum TSH concentration was still high, and therefore the dose of T_4 was increased.

Patient 2 A 51-year-old woman presented with an 8-week history of cold intolerance, constipation, and weight gain. She was found to have hypothyroidism and was treated with T_4, 0.05 mg daily and then 0.1 mg daily. Several weeks later her symptoms worsened. She was noted to have hyperpigmentation but not orthostatic hypotension. Biochemical studies revealed hyponatremia (130 mmol/L), hyperkalemia (5.4 mmol/L), and a normal serum TSH concentration (0.9 mU/L). Serum cortisol concentration was 19.3 µg/dL (533 nmol/L) and plasma ACTH concentration was 84 pg/mL (18 pmol/L). The serum cortisol concentration 60 minutes after a subcutaneous injection of ACTH was 20.8 µg/dL (574 nmol/L), and it increased to only 27.6 µg/dL (763 nmol/L) during a prolonged infusion of ACTH. Plasma renin activity was high and plasma aldosterone concentration was low normal. Tests for antithyroid microsomal and antiadrenal antibodies were positive. This patient also improved promptly in response to glucocorticoid and mineralocorticoid therapy. Six weeks later, while receiving 0.1 mg of T_4 daily her serum TSH concentration was 8.1 mU/L, and therefore the dose of T_4 was increased.

Conclusion Patients with hypothyroidism whose symptoms do not improve or worsen when treated with T_4 may have adrenal insufficiency.

COMMENTARY

It seems likely that these two patients had adrenal insufficiency at the time of diagnosis of hypothyroidism, but that the clues to its presence hyperpigmentation in both patients and postural symptoms in one were overlooked (the occurrence of episodes of hypoglycemia in a well-treated diabetic patient can occur in either disorder, but is probably more common in patients with adrenal insufficiency). Because hypothyroidism is so much more common than adrenal insufficiency, it is easy to attribute nonspecific symptoms such as fatigue and weakness only to the former and to not inquire carefully about pigmentation and check for orthostatic hypotension, much less measure serum sodium, potassium, and cortisol. Indeed, routine measurement of these substances in patients with hypothyroidism is not warranted.

In addition, treatment of hypothyroidism could exacerbate adrenal insufficiency. For one thing, the clearance of cortisol, and no doubt aldosterone, is slowed in patients with hypothyroidism, and increases when the patients are treated with T_4, necessitating an increase in cortisol and aldosterone secretion. A patient with hypothyroidism and subclinical adrenal insufficiency might not be able to increase secretion of these hormones appropriately when treated with T_4, resulting in overt adrenal insufficiency. Also, treatment with T_4 might activate T or B cells sensitized to adrenal antigens, thereby exacerbating autoimmune adrenalitis and decreasing adrenal secretion. In contrast, cortisol deficiency exacerbates chronic autoimmune thyroiditis, and thyroid function often improves or becomes normal during cortisol replacement therapy, presumably due to the immunosuppressive effects of even normal amounts of cortisol. This does not seem to apply to these two patients, because they continued to have high serum TSH concentrations during glucocorticoid therapy.

Robert D. Utiger, M.D.

Few patients with benign thyroid nodules prove to have thyroid carcinoma during follow-up

Liel Y, Ariad S, Barchana M. Long-term follow-up of patients with initially benign thyroid fine-needle aspirations. Thyroid 2001;11:775-8.

SUMMARY

Background Many patients have thyroid nodules, the vast majority of which when biopsied prove to be benign. This raises several questions is the nodule indeed a benign nodule or might the biopsy be falsely negative? Will the nodule change in the future? And is there any way to decrease its size? This study was undertaken to answer the first of these questions.

Methods The study subjects were 578 patients with 631 benign thyroid nodules, based on the results of fine-needle aspiration biopsy guided by palpation, seen at one medical center in Israel between 1979 and 1996. Another 271 patients had biopsies with other results (follicular tumor, 86; suspected carcinoma, 54; carcinoma, 36; inadequate biopsy, 95); no more information is provided about these 271 patients. Among the 578 patients with benign nodules, 344 had solitary nodules and 221 had multinodular goiters on physical examination; the characteristics of the nodules in the remaining 13 patients were not known.

The patients were followed from the time of biopsy to December 31, 1998, or time of death, based on information from the patients records at the medical center supplemented by information from the Israeli Cancer Registry and the National Population Registry. The mean (±SD) duration of follow-up was 8±4 years (range, 1.3 to 19). No information about change in nodule or goiter size or treatment, if any, during follow-up is given. Sixty-six patients had repeat biopsies, done at the discretion of the attending physician.

Results Eight patients (1.4 percent) were found to have a thyroid carcinoma during follow-up. Three of them underwent surgery soon after the biopsy was done; the reasons for surgery are not given and the carcinomas (size not given) may have been incidental findings in patients in whom the dominant nodule was benign. Five patients (0.9 percent) were found to have a thyroid carcinoma 6 or more months (mean, 4.8 years; range, 2 to 10) after the initial biopsy. All had a second biopsy, which was read as benign in one patient (who insisted on having surgery, which revealed follicular carcinoma), follicular tumor in 2 patients, suspected carcinoma in 1 patient, and carcinoma in 1 patient. Two of these patients previously had thyroid surgery, so their nodules may have been new. Thus, of the 66 patients who had repeat biopsies, 4 (6 percent) had results that led to surgery and proved to have carcinoma. How many other patients underwent surgery during follow-up is not stated, but presumably none was found to have a carcinoma.

Conclusion Few patients with thyroid nodules proven to be benign by fine-needle aspiration biopsy prove to have thyroid carcinoma during follow-up.

COMMENTARY

The apparently low rate (1.4 percent) of false negative thyroid biopsies in this group of patients is reassuring, but the method of biopsy and the nature of the follow-up were such that some carcinomas may have been missed. First, the biopsies were guided by palpation rather than ultrasonography, so there is less certainty that the clinically detected nodule was biopsied. In other studies, the proportion of patients whose initial biopsy revealed benign follicular cells but who later proved to have carcinoma ranged from 0 to 14.6 percent. Second, few patients in this study had second biopsies, most likely because of lack of nodule growth. Implicit in this approach is that nodules that do not grow are not carcinomas. However, benign nodules do grow; in the longest (5 years) randomized study of thyroxine therapy, in 83 patients with benign nodules as proven by biopsy at both base line and 5 years, the nodules increased in size in 56 percent of the patients in the control group (and 28 percent of the thyroxine group) (1). And not all carcinomas grow; in a study in which 15 patients with nodules <2 cm (median, 0.9 cm) in diameter that later proved to be papillary carcinomas were followed for 37 months (range, 21 to 85), the median diameter did not change (2).

No one questions the value of fine-needle aspiration biopsy in the initial evaluation of patients with thyroid nodules. Still, the low false negative rate may be misleadingly low for reasons in addition to those cited above. Consider the following, based on the study of Liel et al.: 849 patients had biopsies, which revealed malignant cells, and presumably carcinomas at surgery, in 36 patients (4 percent); and 66 patients had repeat biopsies, which revealed suspicious or malignant cells, and carcinomas at surgery, in 4 patients (6 percent). If 6 percent of the other 512 patients in the group of 578 patients in whom the initial biopsy revealed benign cells also had a carcinoma, that would amount to 31 patients, for a total of 35 patients, nearly as many as the 36 whose initial biopsies revealed malignant cells. There are many reasons not to take these estimates seriously, but they do put the issues of false negative biopsies and follow-up in a different light.

Robert D. Utiger, M.D.

References

1. Papini E, Petrucci L, Guglielmi R, et al. Long-term changes in nodular goiter: a 5-year prospective randomized trial of levothyroxine suppressive therapy for benign cold nodules. J Clin Endocrinol Metab 1998;83:780-3.

2. Asanuma K, Kobayashi S, Shingu K, et al. The rate of tumour growth does not distinguish between malignant and benign thyroid nodules. Eur J Surg 2001;167:102-5.

Increase in breast carcinoma in women with thyroid carcinoma

Chen AY, Levy L, Goepfert H, Brown BW, Spitz MR, Vassilopoulou-Sellin R. The development of breast carcinoma in women with thyroid carcinoma. Cancer 2001;92:225-31.

SUMMARY

Background Several studies have linked different thyroid diseases, including thyroid carcinoma, with carcinoma of the breast, although the biological basis for the linkage is obscure. In the case of thyroid carcinoma, treatment with iodine-131 could be a biological basis for an association with breast carcinoma. Breast tissue has small amounts of sodium/iodide transporters, and therefore in women with thyroid carcinoma treated with I-131, carcinogenic amounts of radioactivity might accumulate in breast tissue. In this study the occurrence of breast carcinoma in women with thyroid carcinoma was investigated using a national cancer database.

Methods The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute contains cancer incidence and survival data from 11 population-based cancer registries covering approximately 15 percent of the U.S. population. Between 1973 and 1995 299,828 women diagnosed with breast carcinoma and 23,080 women diagnosed with thyroid carcinoma were reported to the database. Among them, there were 612 women with both tumors. Women in whom both tumors were diagnosed within 2 years of each other or in whom the tumors were not pathologically confirmed were excluded, leaving 365 women with both breast and thyroid carcinomas. The age- and year-specific incidence rates for thyroid and breast carcinomas were calculated, and the expected number of second carcinomas was calculated based on these incidence rates and the person-years at risk.

Results There were 252 women with thyroid carcinoma who later had breast carcinoma. Their mean (±SD) age at the time of the diagnosis of thyroid carcinoma was 49±14 years (range, 20 to 84), and their mean age at the time of diagnosis of breast carcinoma was 58±13 years (range, 31 to 87); the mean interval was 9±5 years. There were 113 women with breast carcinoma who later had thyroid carcinoma. Their mean age at the time of diagnosis of breast carcinoma was 57±13 years (range, 29 to 94), and their mean age at the time of diagnosis of thyroid carcinoma was 63±13 years (range, 33 to 97); the mean interval was 7±4 years.

Among the 252 women with thyroid carcinoma as the index disease, the expected number of cases of breast carcinoma was 214 (relative risk 1.18; 95 percent confidence interval, 1.04 to 1.33). The risk was limited to premenopausal women, and was greatest 15 to 20 years after the diagnosis of thyroid carcinoma. Among the 113 women with breast carcinoma as the index disease, the expected number of cases of thyroid carcinoma was 115 (relative risk, 0.99; 95 percent confidence interval, 0.81 to 1.18).

Conclusion Among women with thyroid carcinoma, the risk of breast carcinoma is increased slightly.

COMMENTARY

This is the largest study of the occurrence of breast carcinoma in women with thyroid carcinoma; in some previous studies risk was increased and in others it was not. One possible explanation for the results of this study is ascertainment bias women with thyroid carcinoma are likely to be followed more closely than normal women, and therefore a second tumor is more likely to be detected. Arguing against this bias is the lack of an increase in thyroid carcinoma among the women with breast carcinoma. The lack of an increase in thyroid carcinoma in the breast-carcinoma group also argues against the possibility that the occurrence of the two carcinomas was due to some genetic susceptibility.

The possibility that the risk of breast carcinoma might be increased as a result of uptake into breast tissue of small amounts of I-131 given to women to destroy thyroid remnants or treat persistent or recurrent thyroid carcinoma was mentioned above. Only 3 percent of the 252 women whose first tumor was a thyroid carcinoma were reported to have received I-131, but many more must have received it. I-131 therapy has not been identified as a risk factor for breast carcinoma, but external radiation, for example as given to young women to treat Hodgkin s disease, has been. Other possible explanations for an increase in the risk of breast carcinoma in women with thyroid carcinoma are disruption of cyclic pituitary-gonadal function after I-131 therapy (1) or hyperestrogenemia caused by the subclinical or mild overt hyperthyroidism that is often deliberately induced in women with thyroid carcinoma.

Accepting that the risk of breast carcinoma is increased in women with thyroid carcinoma, the magnitude of the risk is so small that surveillance for breast carcinoma in these women need not be more intensive than in normal women of the same age.

Robert D. Utiger, M.D.

References

1. Raymond JP, Izembart M, Marliac V, et al. Temporary ovarian failure in thyroid cancer patients after thyroid remnant ablation with radioactive iodine. J Clin Endocrinol Metab 1989;69:186-90.

Most thyroglossal duct carcinomas are papillary thyroid carcinomas

Doshi SV, Cruz RM, Hilsinger RL Jr. Thyroglossal duct carcinoma: a large case series. Ann Otol Rhinol Laryngol 2001;110:734-8.

SUMMARY

Background The thyroglossal duct originates as a diverticulum at the base of the tongue and extends downward in the neck, sometimes through the hyoid bone, to the first tracheal rings, where it divides to form the lobes of the thyroid gland. A thyroglossal cyst is a cystic expansion of a segment of the thyroglossal duct. The stimulus to formation and expansion of these cysts is unknown, and many are never detected clinically. Occasionally, a carcinoma arises in the thyroglossal duct or a thyroglossal cyst. This study was undertaken to define the characteristics of patients with thyroglossal duct carcinomas seen at a single institution.

Methods and Results 1075 patients with a thyroglossal cyst and 14 patients with a carcinoma of the thyroglossal duct or cyst were identified from the records of the Kaiser Permanente Medical Care Program of Northern California between 1971 and 1995. The 14 patients with a carcinoma consisted of 8 women and 6 men (mean [±SD] age, 39±15 years; range, 22 to 68). The tumor was discovered during a routine examination in 4 patients, 5 had recently noted an enlarging neck mass, 3 had noted a change in a long-standing neck mass, and 2 had neck pain. On physical examination 2 patients had a suprahyoid mass and 12 had a mass between the hyoid bone and the thyroid cartilage. The masses ranged in size from 1 × 0.5 cm to 4.2 × 4 cm. All patients had normal thyroid function. Five patients had fine-needle aspiration biopsies of the mass; 2 aspirates consisted of bloody fluid and 3 revealed papillary-carcinoma cells.

Three patients were treated by excision of the neck mass alone. Eleven patients were treated by excision of the mass, the thyroglossal duct both above and below the hyoid bone, and the midportion of the hyoid bone, a procedure known as the Sistrunk operation. Ten of these patients then underwent thyroidectomy; 2 had microscopic foci of carcinoma in the resected thyroid tissue and 3 had cervical lymph nodes that contained thyroid carcinoma. One patient later had a mediastinal mass that proved to be carcinoma, and another had pulmonary metastases. In several patients the carcinoma was only a small part of the clinically detected neck mass. All the carcinomas were papillary carcinomas. All the patients who underwent thyroidectomy were later treated with radioiodine and thyroid hormone. All 14 patients were alive from 1 month to 17 years after diagnosis.

Conclusion In most patients with thyroglossal duct carcinomas the tumors are papillary thyroid carcinomas, and the patients should be treated in the same way as are patients with papillary carcinomas of the thyroid itself.

COMMENTARY

Thyroglossal duct remnants, including thyroglossal cysts, may be composed of thyroid follicular cells or ductal epithelial cells, and either cell type may give rise to a carcinoma. Approximately 70 percent of patients with thyroglossal cysts are less than 20 years old, but nearly all patients with thyroglossal duct carcinomas are adults. All the patients in this series were adults, and in another series of 12 patients the mean age was 40 years and the youngest patient was 17 years old (1). The clinical manifestations of these carcinomas are similar to those of a thyroglossal cyst. The vast majority are papillary carcinomas, but a few are follicular carcinomas or squamous-cell carcinomas. Patients with papillary carcinomas of the thyroglossal duct may have foci of papillary carcinoma in the thyroid and cervical lymph node metastases at the time of diagnosis, like patients with papillary carcinomas that originate in the thyroid.

In children and adolescents, preoperative biopsy of a midline mass in the upper neck is probably not indicated, given the frequency of thyroglossal cysts and the rarity of thyroglossal duct carcinomas. In adults, however, biopsy is indicated. Because so many of the masses are cystic, it should be done with ultrasound guidance so as to be sure that solid component of the mass is biopsied.

A midline mass located above the thyroid gland that contains carcinoma may also be lymph node containing a metastasis of a thyroid carcinoma or a carcinoma arising in the upper part of a pyramidal lobe. The treatment of all three of these carcinomas is the same, including thyroidectomy and radioiodine therapy, except that in patients with thyroglossal duct carcinomas the surgery should include the Sistrunk procedure. (This procedure was devised after it was realized that simple excision of thyroglossal cysts was often followed by recurrence because the thyroglossal tract often extends almost to the base of the tongue.). An exception would be patients with a microcarcinoma (<1 cm). In them, excision of the mass alone is probably adequate treatment, as is the case in patients with thyroid microcarcinomas.

Robert D. Utiger, M.D.

References

1. Heshmati HM, Fatourechi V, van Heerden JA, et al. Thyroglossal duct carcinoma: report of 12 cases. Mayo Clin Proc 1997;72:315-9.

Histopathological characteristics determine outcome in patients with Hurthle-cell carcinomas

Stojadinovic A, Ghossein RA, Hoos A, Urist MJ, Spiro RH, Shah JP, Brennan MF, Shaha AR, Singh B. Hurthle cell carcinomas: a critical histopathologic appraisal. J Clin Oncol 2001;19:2616-25.

SUMMARY

Background Hurthle cells are large thyroid follicular cells characterized by eosinophilic granular cytoplasm and large hyperchromatic nuclei with a prominent nucleolus. Some benign and malignant thyroid tumors are composed exclusively of Hurthle cells, although these cells are often found in other benign thyroid nodules, chronic autoimmune thyroiditis, and even papillary carcinomas. The distinction between Hurthle-cell adenomas and carcinomas is based on histological, not cytological, characteristics, in particular the presence of capsular and vascular invasion. This retrospective study was undertaken to relate the histopathological characteristics of Hurthle-cell carcinomas with the likelihood of recurrence and death.

Methods Thyroid tumors classified as Hurthle-cell carcinomas were removed from 73 patients at a single cancer center between 1957 and 2000. All the tumors were follicular tumors in which >75 percent of the cells were Hurthle cells arranged in a solid or trabecular, or in a few instances follicular, pattern, and at least partial invasion of the capsule of the tumor was seen in some sections, based on review of a mean of 16 sections per tumor. The tumors were subdivided into three groups: 17 were called tumors of unknown malignant behavior (uncertain carcinomas), in which partial invasion of the capsule but no vascular invasion was seen; 23 were minimally invasive carcinomas, in which a single focus of complete capsular invasion or vascular invasion, or both, was seen; and 33 were widely invasive carcinomas, in which more than one focus of complete capsular invasion or vascular invasion, or both, was seen.

Among the 73 patients, there were 46 women and 27 men (median age, 56 years; range, 9 to 94). The median ages and proportions of women and men in the three groups were similar. All the patients were treated surgically, and some later received radioiodine or external radiation therapy. The median duration of follow-up was 8 years.

Results The median size of the widely invasive carcinomas was 4.5 cm, as compared with 3.0 cm in the other two groups. At the time of initial surgery 19 patients (58 percent) with widely invasive carcinomas had extrathyroidal extension of the tumor, 7 patients (21 percent) had lymph node metastases, and 5 (15 percent) had multiple foci of carcinoma within the thyroid gland, whereas no patient in the other two groups had any of these findings. Among the patients with minimally invasive carcinomas, only two had both capsular and vascular invasion, whereas among those with widely invasive carcinomas, 20 each had >4 foci of capsular and vascular invasion. Furthermore, the vascular invasion was into vessels within the capsule in the 12 patients (52 percent) in the minimally invasive carcinoma group who had any vascular invasion, whereas it was into vessels outside the capsule in all 31 (94 percent) of the patients in the widely invasive carcinoma group who had vascular invasion.

No patient with an uncertain carcinoma or a minimally invasive carcinoma had any local recurrence or metastases or died from their disease. Among those with widely invasive carcinoma, 24 (73 percent) had local recurrences, 21 (64 percent) had metastases, and 18 (54 percent) died of their disease. In this group the median recurrence-free survival was 28 months and the median disease-specific survival was 86 months; the 10-year disease-specific survival was 48 percent. Factors associated with poor survival were extrathyroidal extension of the carcinoma and lymph node metastases at diagnosis, but not age or size of the carcinoma.

Conclusion Capsular and especially vascular invasion are major determinants of outcome in patients with Hurthle-cell carcinomas of the thyroid gland.

COMMENTARY

Hurthle-cell carcinomas were once thought to be rare, but they now are the third most common type of thyroid carcinoma. Among 5583 cases of thyroid carcinoma reported by over 1500 hospitals in the United States in 1996, 80.9 percent were papillary carcinomas, 10.4 percent were follicular carcinomas, 3.7 percent were Hurthle-cell carcinomas, 3.2 percent were medullary carcinomas, and 1.7 percent were anaplastic carcinomas (1).

Biologically, Hurthle-cell carcinomas most closely resemble follicular carcinomas, and the criteria for diagnosis of the two types of carcinoma are similar, being based on the presence of capsular and vascular invasion by tumor cells rather than the cytological characteristics of the cells. What seems clear from this study is that tumors that only partially invade the capsule of the tumor should not be called carcinomas at all. The distinction between minimally and widely invasive carcinomas in terms of outcome certainly seems real, and would mandate different treatment. For example, patients with minimally invasive carcinomas would not need completion thyroidectomy or radioiodine therapy, whereas both would be indicated in patients with widely invasive carcinomas.

Robert D. Utiger, M.D

References

1. Hundahl SA, Cady B, Cunningham MP, et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. Cancer 2000; 89:202-17.

Diagnostic iodine-131 scans do not reduce the efficacy of initial iodine-131 therapy in patients with thyroid carcinoma

Morris LF, Waxman AD, Braunstein GD. The nonimpact of thyroid stunning: remnant ablation rates in ^{131}I-scanned and nonscanned individuals. J Clin Endocrinol Metab 2001;86:3507-11.

SUMMARY

Background Many patients with differentiated thyroid carcinoma undergo diagnostic thyroid scanning with iodine-131 (I-131) after initial surgical treatment to determine if they have some residual normal thyroid tissue or thyroid carcinoma in lymph nodes in the neck or elsewhere. If either is present, the patients are then given a high dose of I-131. Some evidence suggests that the relatively low doses (3 to 6 mCi [111 to 222 MBq]) of I-131 given for diagnostic scanning may damage ("stun") some of the remaining normal thyroid or carcinoma tissue, so that less of a subsequent therapeutic dose of I-131 is taken up, thereby reducing the efficacy of the therapeutic dose. This retrospective study was undertaken to determine if diagnostic imaging does indeed reduce the efficacy of subsequent high doses of I-131 in destroying residual normal thyroid or thyroid-carcinoma tissue.

Methods The effect of whole-body diagnostic I-131 scanning on the effect of initial I-131 therapy was studied in 100 patients, 37 of whom underwent diagnostic scans and 63 of whom did not. The diagnostic scans had been eliminated in 1994 because the benefits were thought to be limited and outweighed by the inconvenience of the test and the possibility of stunning. The diagnostic-scan group consisted of 22 women and 15 men; their mean (±SD) age was 40±14 years. The no-diagnostic-scan group consisted of 43 women and 20 men; their mean age was 43±14 years. Most patients (35 in the diagnostic-scan group and 60 in the no-diagnostic-scan group) had papillary carcinoma. All the patients had recently undergone thyroidectomy and were receiving their first dose of I-131, primarily to destroy any remaining normal thyroid tissue. The I-131 doses for diagnostic scanning ranged from 3 to 6 mCi (111 to 222 MBq); I-131 therapy was given 2 to 5 days later. The therapeutic doses of I-131 in both groups ranged from 100 to 200 mCi (3700 to 7400 MBq). All patients had whole-body scans 2 and 7 to 10 days after treatment. The efficacy of therapy was determined by evaluation of whole-body diagnostic thyroid scans done 4 to 42 months (mean, 12) later. The patients were advised to eat a low iodine diet before each scan or treatment, and all had high serum thyrotropin concentrations at these times.

Results The follow-up I-131 scans 4 to 42 months later revealed no uptake in the thyroid bed in 24 (65 percent) of the patients in the diagnostic-scan group and 42 (67 percent) of the patients in the no-diagnostic-scan group (P=0.85). The proportion of patients in whom there was no uptake did not vary as a function of the therapeutic dose of I-131. In the diagnostic-scan group, the initial diagnostic scans revealed I-131 uptake outside the thyroid bed in 9 patients (24 percent), of whom 6 (67 percent) had no uptake on the follow-up scan. In the no-diagnostic-scan group, the initial posttreatment scans revealed uptake outside the thyroid bed in 23 patients (36 percent), of whom 18 (78 percent) had no uptake on the follow-up scan. In nearly all patients, the uptake outside the thyroid bed was thought to be in lymph nodes in the neck. The efficacy of I-131 therapy in destroying thyroid tissue either in the thyroid bed or elsewhere was not related to the treatment dose.

Conclusion In patients with thyroid carcinoma, the efficacy of initial I-131 therapy in destroying thyroid remnants or metastases is not reduced by diagnostic I-131 scanning.

COMMENTARY

The precise definition of stunning is that administration of a low dose of I-131 for detection of thyroid remnants or residual or metastatic thyroid carcinoma damages the normal or abnormal thyroid tissue so that it takes up less of a subsequent high dose of I-131, as determined by comparison of diagnostic and posttreatment scans. The reduced uptake by normal or abnormal thyroid tissue on a posttreatment scan implies that the tissue is less likely to be destroyed by the treatment dose, as compared with tissue that took up I-131 well after administration of both diagnostic and treatment doses. However, the detection of stunning depends at least in part on several technical issues. It is, for example, detected more often when the treatment dose is given soon after the diagnostic dose and when the posttreatment scan is done 2 to 4 days after treatment, as compared with later. The use of a lower dose of I-131, for example 2 mCi (74 MBq), for diagnostic scanning in order to minimize stunning, leads to detection of fewer foci of residual or metastatic carcinoma, thereby potentially providing less information about the extent of the disease.

The really important question is not whether the normal or abnormal thyroid tissue is as visible on a posttreatment scan as on a diagnostic scan, but whether that tissue is destroyed by the I-131 treatment. In this study, the efficacy of I-131 treatment, whether given to destroy normal thyroid tissue or thyroid carcinoma, was not reduced by diagnostic scanning with I-131. However, diagnostic scans before initial I-131 treatment provide little useful information, and rarely alter subsequent treatment. For those who think diagnostic scans are useful and continue to worry about stunning, the solution is to scan with I-123 rather than I-131 (1).

Robert D. Utiger, M.D.

References

1. Mandel S, Shankar LK, Benard F, et al. Iodine-123 is superior to iodine-131 in detecting thyroid remnants in patients with differentiated thyroid carcinoma. Clin Nucl Med 2001;26:6-9.

Thyroid autoimmune disease in Turner s syndrome is most commonly associated with an X-isochromosome karyotype

Elsheikh M, Wass JAH, Conway GS. Autoimmune thyroid syndrome in women with Turner s syndrome the association with karyotype. Clin Endocrinol 2001;55:223-6.

SUMMARY

Background Turner s syndrome is characterized by absence of a sex chromosome (45,X), sex chromosome mosaicism (for example 45,X/46,XX or 45,X/46,XY), or an abnormal X chromosome, including an X isochromosome (loss of the short arm and duplication of the long arm of an X chromosome, 46,X,isoXq) or a ring X chromosome (46,X,rX). Autoimmune thyroid disease is common in patients with Turner s syndrome, and in some studies was most common in patients with an X isochromosome. This study was undertaken to determine the frequency of autoimmune thyroid disease and the relationship between thyroid disease and karyotype in a large group of patients with Turner s syndrome.

Methods The study subjects were 145 women (mean age, 26 years; range, 16 to 52) with Turner s syndrome, as defined by karyotype analysis of peripheral blood leukocytes, who were attending clinics for adult women with the syndrome. Serum antithyroid microsomal antibodies and antithyroglobulin antibodies were measured by agglutination assays; the results were considered positive if the antibodies were present in serum diluted more than 160-fold. Serum thyrotropin (TSH) was measured by immunoassay. Autoimmune thyroid disease was defined as a high or low serum TSH concentration and a positive test for one or both types of antibodies, based on single measurements probably done at the time of the first clinic visit.

Results Among the 145 women, 60 (41 percent) had positive tests for antithyroid microsomal or antithyroglobulin antibodies, or both. Thirty-three women (23 percent) had positive tests for antithyroid microsomal antibodies, 3 (2 percent) had positive tests for antithyroglobulin antibodies, and 24 (16 percent) had positive tests for both antibodies. Twenty-two women (15 percent) had overt or subclinical hypothyroidism, and 1 (1 percent) had Graves hyperthyroidism. The frequency of goiter is not stated. At the time of diagnosis of hypothyroidism the women ranged in age from 9 to 42 years (median, 18).

The majority of the women (59 percent) had a 45,X karyotype, but the proportions of women with positive tests for thyroid antibodies and autoimmune thyroid disease were highest in those with a 46,X,isoXq karyotype (table). The ages of the women in each of the five subgroups were similar.

Table. Thyroid Antibodies and Thyroid Autoimmune Disease in Women with Turner s Syndrome.

Karyotype	No. of Women	No. (%) with Positive Tests for Thyroid Antibodies	No. (%) with Thyroid Autoimmune Disease
45,X	86	35 (41)	12 (14)
46,X,isoXq	24	20 (83)	9 (38)
45,X/46,XX	15	0 (0)	0 (0)
45,X/46,XY	10	2 (20)	1 (10)
45,X/46X,rX	10	3 (30)	1 (10)
Total	145	60 (41)	23 (16)

Conclusion Among women with Turner s syndrome those with a 46,X,isoXq karyotype are most likely to have positive tests for antithyroid antibodies and thyroid autoimmune disease.

COMMENTARY

Autoimmune thyroid disease, whether defined as the presence of antithyroid antibodies alone or combined with thyroid dysfunction (nearly always hypothyroidism) as in this study, is known to be common in patients with Turner s syndrome. It occurs at a young age; in one study antithyroid antibodies were detected in 46 of 89 girls aged 3 to 16 years (52 percent), as compared with 34 of 199 age-matched normal girls (17 percent) (1). The frequency of positive tests for antithyroid antibodies and the serum titers or concentrations of the antibodies (not reported in this paper) increase with age in these patients, as does the frequency of hypothyroidism. Based on this and other studies, patients with 46,X,isoXq or 46,X karyotypes are most likely to have autoimmune thyroid disease (1,2). These are the most common karyotypes, and they are the ones most likely to be associated with the classic manifestations of Turner s syndrome, including short stature, sexual infantilism and somatic anomalies. The association between these two karyotypes and autoimmune thyroid disease indicates that loss of one or more genes (haploinsufficiency) on the short arm of the X (or Y) chromosome that are not normally inactivated is important in the pathogenesis of the thyroid disease. The frequency of other autoimmune endocrine disorders does not seem to be increased in patients with either of these karyotypes or those with Turner s syndrome in general.

Robert D. Utiger, M.D.

References

1. Ivarrson SA, Ericsson UB, Nilsson KO, et al. Thyroid autoantibodies, Turner s syndrome and growth hormone therapy. Acta Pediatr 1995;84:63-5.

2. Chiovato L, Larizza D, Bendinelli G, et al. Autoimmune hypothyroidism and hyperthyroidism in patients with Turner s syndrome. Eur J Endocrinol 1996;134: 568-75.

Fetal DNA is present in thyroid tissue of women with Hashimoto s disease

Klintschar M, Schwaiger P, Mannweiler S, Regauer S, Kleiber M. Evidence of fetal microchimerism in Hashimoto s thyroiditis. J Clin Endocrinol Metab 2001;86:2494-8.

SUMMARY

Background Fetal cells migrate into the circulation of pregnant women during gestation, which may be important in inducing maternal tolerance to the fetus. Cells that are differentiated, such as nucleated red cells and trophoblast cells, disappear soon after delivery, but fetal stem cells may persist for many years. After delivery, the cells can be found not only in maternal serum, but also may differentiate and migrate into various maternal tissues. Thus, the woman becomes a chimera, with two or more genetically distinct cell lines. This microchimerism, so termed because there are only a few fetal cells, is most readily identified by detection of Y-chromosomal material. Autoimmune diseases have been linked to microchimerism, and Y-chromosomal material has been detected in the peripheral blood and skin lesions of women with scleroderma. This study was undertaken to determine if Y-chromosomal material could be detected in thyroid tissue of women with Hashimoto s thyroiditis (goitrous autoimmune thyroiditis).

Methods Y-chromosomal material was sought in thyroid tissue from 17 women with Hashimoto s thyroiditis and 25 women with a nodular goiter. DNA extracted from paraffin-embedded tissue was amplified by the polymerase chain reaction in two ways. One used primers surrounding the SRY gene critical for male development. The second used primers for a fragment of the amelogenin gene. This gene, which codes for a protein in tooth matrix. is found on both X and Y chromosomes, but the fragment amplified from the X chromosome has 106 base pairs (bp) and that from the Y chromosome 112 bp. This allows estimation of the relative proportion of Y-chromosomal material in a tissue sample. No information is provided about the thyroid function, indications for surgery, or pathological findings in the women in either group.

Results SRY gene material was detected in thyroid tissue in 8 (47 percent) of the 17 women with Hashimoto s disease, as compared with 1 of the 25 women with a nodular goiter (4 percent). Y-chromosome-derived amelogenin gene material was found in the thyroid tissue of 4 of the 8 women with Hashimoto s disease with SRY micro-chimerism, but none of the other women with Hashimoto s disease and none of the women with a nodular goiter. The ratios of Y to X gene material were very low; the highest ratio was 0.045, indicating the presence of only a few male cells.

The mean (±SD) age of the women with Hashimoto s disease was 47±9 years, and that of the women with a nodular goiter was 54±7 years. The mean number of offspring was 2±1 per woman and the mean number of sons was 1±1 per woman in both groups; information about pregnancies was missing for 4 women with Hashimoto s disease and 9 women with a nodular goiter. Among the 13 women with Hashimoto s thyroiditis for whom pregnancy information was available, all 7 with thyroid microchimerism had delivered at least one son 12 to 46 years before diagnosis. So too had 4 of the 6 women with no thyroid microchimerism (4 to 33 years before diagnosis); the other 2 had no children. The former group also had more children (3 vs. 1 per woman) and more daughters (1 vs. 0.2 per woman).

Conclusion In some women with Hashimoto s thyroiditis the thyroid tissue contains Y-chromosomal material indicative of fetal microchimerism.

COMMENTARY

Accepting that there is engraftment of fetal cells into the mother s thyroid tissue, Hashimoto s thyroiditis may be a form of graft versus host disease in which the engrafted fetal cells initiate the inflammatory reaction that ultimately destroys the thyroid gland. The apparently small numbers of grafted cells need not cause all the damage, but only initiate it; host cells then perpetuate it. Alternatively, the grafted cells might cause host T cells to lose tolerance to host thyroid follicular cells and therefore to reject them. If engraftment is important, it should be detected in the thyroid of most women with Hashimoto s disease. It was not, perhaps because the methods for detecting it are not very sensitive. It could also be an epiphenomenon, just as are high serum concentrations of antithyroid peroxidase and antithyroglobulin antibodies.

Assuming engraftment is important, one determinant of susceptibility to Hashimoto s disease might be the ease with which the fetal cells gain access to thyroid tissue. Another might be the number of opportunities for cell transfer and therefore engraftment, for example the number of pregnancies or blood transfusions. Among the women with Hashimoto s disease in this study, those in whom thyroid microchimerism was detected had more sons and more daughters than those without microchimerism. There must be other determinants of susceptibility, given the similar pregnancy histories in the women with Hashimoto s disease and those with a nodular goiter. Also, Hashimoto s disease undoubtedly occurs in women who were never pregnant, and it certainly does occur in prepubertal children and occasionally in men. There are, however, no epidemiological studies examining the relationships between these characteristics and Hashimoto s disease in large groups of people.

Postpartum thyroiditis is known to predispose to Hashimoto s thyroiditis. Is it possible that it as well as Hashimoto s disease results from engraftment of fetal cells in the thyroid?

Robert D. Utiger, M.D.

High frequency of gestational changes in thyroid and thyrotropin secretion in Asian women

Yeo CP, Khoo DHC, Eng PHK, Tan HK, Yo SL, Jacob E. Prevalence of gestational thyrotoxicosis in Asian women evaluated in the 8th to 14th weeks of pregnancy: correlations with total and free beta human chorionic gonadotrophin. Clin Endocrinol 2001;55:391-8.

SUMMARY

Background Thyroid function changes during pregnancy in several ways. Serum concentrations of thyroxine-binding globulin (TBG) increase, causing increases in serum total thyroxine (T_4) and total triiodothyronine (T_3) concentrations that persist until delivery. Adaptation to this increase in serum TBG concentrations requires an increase in thyrotropin (TSH) secretion and in thyroid secretion. In addition, the high serum human chorionic gonadotropin (HCG) concentrations present from approximately 6 to 16 weeks of gestation independently stimulate thyroid secretion, thereby slightly raising serum free T_4 and free T_3 concentrations and slightly decreasing serum TSH concentrations. High serum free T_4 and free T_3 concentrations or low serum TSH concentrations, as compared with the values in normal nonpregnant women and in men, may be more common among pregnant Asian than white women. This cross-sectional study was undertaken to determine the frequency of these abnormalities in Chinese and Malay women living in Singapore.

Methods Serum free T_4, free T_3, TSH, HCG, and HCG beta-subunit were measured by immunoassays in 184 consecutive Singaporean women who were 8 to 14 weeks pregnant. The results were compared with those in 500 normal nonpregnant women and men. Serum TSH-receptor antibodies were measured by receptor assay in women with high serum free T_4 concentrations or low serum TSH concentrations.

Results Two of the women (1 percent) had high serum free T_4, low serum TSH, and high serum TSH-receptor antibody concentrations and were considered to have Graves hyperthyroidism. Among the other 182 women, serum free T_4 and free T_3 concentrations were high in 27 (15 percent) and 6 (3 percent), respectively, and serum TSH concentrations were low in 60 (33 percent). Twenty women (11 percent) had both high serum free T_4 and low serum TSH concentrations; these women were considered to have gestational hyperthyroidism. Serum HCG and HCG beta-subunit concentrations were positively correlated with serum free T_4 concentrations and negatively correlated with serum TSH concentrations ($P<0.01$ for all correlations). The prevalence of high serum free T_4 and low serum TSH concentrations was 14 percent in the women who were 8 to 11 weeks pregnant and 5 percent in those who were 12 to 14 weeks pregnant; the serum HCG and HCG beta-subunit concentrations were higher in the former group.

Conclusion Eleven percent of pregnant women in Singapore have high serum free T_4 and low serum TSH concentrations.

COMMENTARY

In pregnant women. high serum free T_4 concentrations and low serum TSH concentrations, or either alone, rarely indicate the presence of any thyroid dysfunction, but are instead caused by the thyroid-stimulating action of the indispensable pregnancy hormone HCG. It stimulates thyroid secretion enough to lower TSH secretion, but the increase in thyroid secretion is small and transient. Thus, the term *gestational hyperthyroidism* seems inappropriate, because it implies thyroid dysfunction, whereas in fact the normal reference ranges for serum free T_4, free T_3, and TSH concentrations change slightly in pregnant women. Indeed, these ranges change almost weekly during early pregnancy, as suggested by the results at different times of pregnancy in this cross-sectional study and documented by serial studies (1). If a descriptive term is necessary, *gestational hyperthyroxinemia* would be better.

In an earlier study, more Indian and Pakistani women than white women who were 15 or 16 weeks pregnant had low serum TSH concentrations (16 vs. 5 percent) (2). Here, Chinese and Malay women living in Singapore were studied, but no white women, whether living in Singapore or elsewhere, were studied using the same assays. In a study of Japanese women who were 6- to 14-weeks pregnant the frequency of high serum free T_4 and low serum TSH concentrations was only 0.3 percent (3).

Very high serum HCG concentrations can cause marked thyroid hypersecretion, and if the HCG stimulation persists, clinically important hyperthyroidism can occur. This is most evident in women with trophoblastic tumors who characteristically have very high serum HCG concentrations. Serum HCG concentrations also are high in women with multiple pregnancies and women with hyperemesis gravidarum, as compared with normal women with singleton pregnancies, and more of the women in those two groups have low serum free T_4 concentrations for longer periods of time.

Robert D. Utiger, M.D.

References

1. Glinoer D. The regulation of thyroid function in pregnancy: pathways of adaptation from physiology to pathology. Endocr Rev 1997;18:404-33.

2. Price A, Davies R, Heller SR, et al. Asian women are at increased risk of gestational thyrotoxicosis. J Clin Endocrinol Metab 1996;81:1160-3.

3. Tanaka D, Yamada H, Kato EH, et al. Gestational transient hyperthyroxinaemia (GTH): screening for thyroid function in 23,163 pregnant women using dried blood spots. Clin Endocrinol 1998;49: 325-9.

Carbamazepine and oxcarbazepine, but not valproic acid, slightly reduce serum thyroxine concentrations in men with epilepsy

Isojarvi JIT, Turkka J, Pakarinen AJ, Kotila M, Rattya J, Myllyla VV. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. Epilepsia 2001;42:930-4.

SUMMARY

Background Antiepileptic drugs such as phenytoin and carbamazepine tend to reduce serum total and free thyroxine (T_4) concentrations slightly, but their effects on other aspects of pituitary-thyroid function have been inconsistent, perhaps because of variations in duration of treatment. This study was undertaken to determine the effects of long-term carbamazepine and oxcarbazepine monotherapy in men with epilepsy. A group of men with epilepsy taking valproic acid was studied for comparison.

Methods The study subjects were 90 men with epilepsy aged 18 to 50 years, of whom 40 were taking carbamazepine, 29 oxcarbazepine, and 21 valproic acid. Only men taking a single antiepileptic drug were included, and those with other illnesses or taking other drugs were excluded. Most of the men in the carbamazepine and oxcarbazepine groups had partial epilepsy, whereas the majority of the men in the valproic acid group had primary generalized epilepsy. The mean duration of treatment was 9 years in the carbamazepine group, (mean dose, 641 mg daily), 2 years in the oxcarbazepine group (mean dose, 1071 mg daily), and 5 years in the valproic acid group (mean dose, 1219 mg daily). Serum total and free T_4, total triiodothyronine (T_3), thyrotropin (TSH), γ-glutamyltransferase (a marker of hepatic enzyme activity), and the relevant antiepileptic drug were measured in each man. The results were compared with those in 25 normal men aged 32 to 46 years.

Results The mean serum total and free T_4 concentrations were lower in the men in the carbamazepine and oxcarbazepine groups, but not the valproic acid group, as compared with the normal men (table). Serum total and free T_4 concentrations were below the reference range in 20 men (50 percent) and 5 men (12 percent), respectively, in the carbamazepine group, and 6 men (21 percent) and 3 men (10 percent), respectively, in the oxcarbazepine group. None of the men in the valproic acid group had low values for either measurement. There were no differences in serum T_3 and TSH concentrations among the four groups, and no man had low values for either of these measurements. Serum γ-glutamyltransferase concentrations were high in the men in the carbamazepine and oxcarbazepine groups, but were not correlated with the serum total or free T_4 concentrations.

Table. Mean (±SD) Serum Thyroid Hormone and TSH Concentrations in Men with Epilepsy and Normal Men.

	No.	Serum T_4 (μg/dL)	Serum Free T_4 (ng/dL)	Serum T_3 (ng/dL)	Serum TSH (μU/mL)
Carbamazepine	40	5.1±1.0*	1.0±0.1*	124±20	1.7±0.9
Oxcarbazepine	29	5.5±0.7*	1.0±0.1*	124±20	1.5±0.7
Valproic acid	21	6.1±0.8	1.1±0.1	130±20	2.4±1.1
Normal men	25	6.7±0.9	1.1±0.1	124±20	1.9±1.4

*P≤0.01, as compared with normal men.
To convert serum total and free T_4 values to nmol/L and pmol/L, respectively, multiply by 12.9; and to convert serum T_3 values to nmol/L, multiply by 0.0154.

Conclusion Men with epilepsy treated with carbamazepine or oxcarbazepine have slightly low serum total and free T_4 concentrations but no change in serum TSH concentrations, suggesting that the drugs inhibit TSH secretion, whereas valproic acid has no effect on pituitary-thyroid function.

COMMENTARY

This is perhaps the most comprehensive study of carbamazepine in patients with epilepsy, but oxycarbazepine has been studied hardly at all. In nearly all studies the carbamazepine-treated patients had slightly lower serum total and free T_4 concentrations than normal subjects, but some patients had slightly low serum T_3 concentrations or slightly high serum TSH concentrations, and in one study their thyroid volume was slightly larger (1). The decrease in serum T_4 concentrations is usually attributed to the ability of these drugs (also including phenytoin) to stimulate hepatic enzyme activity, thereby increasing T_4 clearance. Isojarvi et al. contend that hepatic enzyme induction is not responsible for the changes in serum T_4 concentrations, because they found no (inverse) correlation with serum γ-glutamyltransferase concentrations. They suggest instead that the primary effect of the drugs is to inhibit TSH secretion. However, that suggestion is not compatible with the observations of increases in TSH secretion and thyroid size, or the increase in TSH secretion that has been described in T_4-treated hypothyroid patients given carbamazepine or phenytoin.

Do the patients with slightly low serum free T_4 concentrations have central hypothyroidsm. Perhaps, but in a crossover study of T_4 and placebo there were no differences in a clinical score for hypothyroidism or cardiac contractility at the end of either treatment period (2).

Robert D. Utiger, M.D.

References

1. Hegedus L, Hansen JM, Luhdorf K, et al. Increased frequency of goiter in epileptic patients on long-term phenytoin or carbamazepine treatment. Clin Endocrinol 1985;23:423-9.

2. Tiihonen M, Liewendahl K, Waltimo O, et al. Thyroid status of patients receiving long-term anticonvulsant therapy assessed by peripheral parameters: a placebo-controlled thyroxine therapy trial. Epilepsia 1995;36:1118-25.

Interferon-β does not cause thyroid dysfunction or autoimmunity

Durelli L, Ferrero B, Oggero A, Verdun E, Ghezzi A, Montanari E, Zaffaroni M, and the Betaferon Safety Trial Study Group. Thyroid function and autoimmunity during interferon β-1b treatment: a multicenter prospective study. J Clin Endocrinol Metab 2001;86:3525-32.

SUMMARY

Background Administration of interferon-α is known to activate autoimmune thyroid disease and cause painless (silent) lymphocytic thyroiditis with transient hyperthyroidism, transient hypothyroidism, or both, and occasionally permanent hypothyroidism or Graves hyperthyroidism. In some studies administration of interferon-β had similar effects in a few patients, but the frequency and the extent of the changes have not been well studied. The purpose of this study was to determine the frequency of thyroid dysfunction and autoimmunity in a large group of patients with multiple sclerosis treated with interferon-β.

Methods The study subjects were 156 patients (101 women and 55 men; mean age, 32 years range, 18 to 49) with relapsing-remitting multiple sclerosis for 10 years (range, 2 to 27). The patients were treated with 8×10^6 units of interferon-β-1b given subcutaneously every other day for 12 months. Patients with thyroid disease were not excluded, but those with clinically important cardiovascular, renal, and liver disease were excluded. Serum thyrotropin (TSH), free thyroxine (T_4), free triiodothyronine (T_3), and antithyroglobulin and antithyroid microsomal antibodies were measured before and twice during the first month of treatment, after 2 and 3 months, and then every 3 months for 12 to 15 months, or until an exacerbation of multiple sclerosis occurred or treatment was stopped because of adverse effects. Not all patients had all measurements at each time. The results were compared with the results in 437 normal subjects (162 women and 275 men).

Results At base line, the frequency of thyroid dysfunction and high serum concentrations of antithyroid microsomal antibodies was similar in the patients with multiple sclerosis and the normal subjects. During interferon-β-1b treatment, no patient had onset of overt or subclinical hypothyroidism; 1 patient (0.6 percent) had subclinical hypothyroidism at base line that persisted during treatment. At base line, 8 patients (5 percent) had low serum TSH concentrations; the frequency after treatment for 3, 6, 9, and >9 months was 9 (6 percent), 4 (4 percent), 4 (3 percent), and 10 (8 percent), respectively. All but 3 of these patients had subclinical hyperthyroidism. The probability of having a low serum TSH concentration did not increase with time. Patients with low serum TSH concentrations at base line were more likely to have persistently low concentrations than those whose concentrations became low during treatment.

The serum concentrations of antithyroid microsomal antibodies, antithyroglobulin antibodies, or both, were high in 15 patients (10 percent) at baseline, and in 13 patients (9 percent) at 3 months, 14 patients (11 percent) at 6 months, 12 patients (9 percent) at 9 months, and 10 patients (8 percent) at >9 months. (Serum concentrations of antithyroid microsomal antibodies were higher more often than those of antithyroglobulin antibodies.) Only 5 patients who had normal serum concentrations of both antibodies at baseline had high concentrations on one or more occasions during treatment, and the probability of having a high serum concentration of either antibody did not increase with time during treatment. Patients with high serum antithyroid microsomal or antithyroglobulin antibody concentrations at base line were more likely to have persistently high concentrations than were patients who first had high concentrations during treatment.

There was no correlation between high serum antithyroid microsomal or antithyroglobulin antibody concentrations at base line or during treatment and the occurrence of thyroid dysfunction during treatment.

Conclusion Among patients with multiple sclerosis, treatment with interferon-β-1b is not associated with thyroid dysfunction or thyroid autoimmunity.

COMMENTARY

Not all interferons are alike. Interferon-α, given most often to patients with hepatitis B or C infection or various tumors, seems to induce production of thyroid antibodies and cause transient if not permanent thyroid dysfunction. These changes occur in approximately 10 to 15 percent of patients with chronic hepatitis C infection, especially in those with preexisting thyroid autoimmunity (1). In contrast, interferon-β, given most often to patients with multiple sclerosis, does not cause thyroid autoimmunity or thyroid dysfunction. Finally, interferon-γ, perhaps best known for its ability to induce expression of major histocompatibility complex (MHC) class II molecules on epithelial cells, including thyroid follicular cells, which might be expected to induce autoimmune thyroid disease, does not cause thyroid autoimmunity or thyroid disease (2). At a practical level, patients treated with interferon-α, but not interferon-β, should be monitored periodically for thyroid dysfunction.

Robert D. Utiger, M.D.

References

1. Fernandez-Soto L, Gonzalez A, Escobar-Jimenez F, et al. Increased risk of autoimmune thyroid disease in hepatitis C vs hepatitis B before, during and after discontinuing interferon therapy. Arch Intern Med 1998;158:1445-8.

2. Kung AWC, Jones BM, Lai CL. Effects of interferon-γ therapy on thyroid function, T-lymphocyte subpopulations and induction of autoantibodies. J Clin Endocrinol Metab 1990;71:1230-4.

Artifactual elevations in serum free thyroxine and triiodothyronine concentrations during heparin therapy

Laji K, Rhidha B, John R, Lazarus J, Davies JS. Abnormal serum free thyroid hormone levels due to heparin administration. QJM 2001;94:471-3.

SUMMARY

Background Administration of heparin can transiently increase serum free thyroxine (T_4) and free triiodothyronine (T_3) concentrations. This increase may be mistaken to indicate the presence of hyperthyroidism, especially in patients who may have low serum thyrotropin (TSH) concentrations as a result of nonthyroidal illness. This case study describes four patients treated with unfractionated or low-molecular-weight heparin who had high serum free T_4 and free T_3 concentrations, as determined by immunoassay.

Case Reports

Patient 1 was a 62-year-old woman who was hospitalized because of progressive leg weakness and pain. She was given tinzaparin, 3400 units subcutaneously daily, to prevent venous thromboembolism. When measured 48 hours after admission her serum free T_4 concentration was high and her serum free T_3 concentration was high normal (table). She was subsequently determined to have diabetic amyotrophy.

Patient 2 was a 42-year-old woman who was hospitalized for evaluation of pleuritic chest pain. She had a history of pulmonary embolism, and recurrent embolism was suspected. She was treated with heparin, 5000 units intravenously. Serum free T_4 and T_3 concentrations measured 12 hours later were high (table). After discontinuation of heparin the values were normal.

Table. Serum Free T_4, Free T_3 and TSH Concentrations during Treatment with Heparin.

	Patient 1	Patient 2	Patient 3	Patient 4	Reference Range
Serum free T_4 (ng/dL)	2.7	4.6	5.4	2.6	0.8-1.8
Serum free T_3 (ng/dL)	0.4	0.7	0.7	0.7	0.2-0.4
Serum TSH (mU/L)	0.9	3.0	1.0	1.8	0.4-5.5

To convert serum free T_4 and free T_3 values to pmol/L, multiply by 12.9 and 0.0154, respectively.

Patient 3 was a 40-year-old man with an astrocytoma who was hospitalized for dyspnea, chest pain, and atrial fibrillation. Thromboembolic disease was suspected. During treatment with tinzaparin, 20,000 units subcutaneously daily, he had high serum free T_4 and free T_3 concentrations (table).

Patient 4 was a 41-year-old woman who was hospitalized for chest pain and atrial fibrillation. Pulmonary embolism was suspected. She was treated with intravenous heparin, and then found to have high serum free T_4 and free T_3 concentrations (table).

Measurements of serum free T_4 and free T_3 using another immunoassay in 2 of the patients also revealed high values. All 4 patients had normal serum TSH concentrations.

Conclusion Unfractionated and low-molecular-weight heparin can cause artifactual elevations in serum free T_4 and free T_3 concentrations.

COMMENTARY

This study serves a reminder that patients receiving heparin and its low- molecular-weight derivatives can have high serum free T_4 and free T_3 concentrations, as measured by different assays, including equilibrium dialysis (1,2). Intravenous and subcutaneous administration of heparin increases lipase activity; the activated lipase catalyzes hydrolysis of serum triglycerides; and the free fatty acids produced by the hydrolysis inhibit binding of T_4 and T_3 to albumin and perhaps other thyroid transport proteins, thus acutely raising serum free T_4 and free T_3 concentrations. The increase in lipase activity occurs very soon and persists for hours after heparin administration, but serum free fatty acid concentrations do not rise sufficiently in vivo to affect T_4 and T_3 binding. In vitro, however, serum free fatty acid concentrations increase with time, because they cannot be cleared. This effect of heparin to raise serum free T_4 and free T_3 concentrations is most prominent in serum samples that are collected several hours after heparin administration and then are kept at room temperature or higher for hours before or during the analyses. The effect is exaggerated in patients who have high serum triglyceride concentrations, because more free fatty acids can be generated, and in patients with low serum albumin concentrations, because there are fewer binding sites for free fatty acids or T_4 and T_3. Since the change occurs in vitro, serum total T_4 and total T_3 concentrations are not altered.

This artifact can be avoided by collecting blood samples for measurements of serum free T_4 and free T_3 10 to 12 hours, or more, after administration of heparin or low-molecular-weight heparin. It can also be avoided by prompt analysis after collection, by storage of samples at low temperatures before analysis, or by addition of protamine to blood samples soon after they are collected.

Robert D. Utiger, M.D.

References

1. Jaume JC, Mendel CM, Frost PH, et al. Extremely low doses of heparin release lipase activity into the plasma and can thereby cause artifactual elevations in the serum-free thyroxine concentration as measured by equilibrium dialysis. Thyroid 1996;6:79-83.

2. Stevenson HP, Pooler G, Archbold R, et al. Misleading serum free thyroxine results during low molecular weight heparin treatment. Clin Chem 1998; 44:1002-7.

Perchlorate in drinking water in Nevada is not associated with thyroid disease

Li FX, Squartsoff L, Lamm SH. Prevalence of thyroid diseases in Nevada counties with respect to perchlorate in drinking water. J Occup Environ Med 2001;43:630-4.

SUMMARY

Background Perchlorate salts, which are constituents of some fertilizers, as well as propellants for rockets, fireworks, flares, and air-bag inflation systems, have been found in the water supply in some communities in about a dozen states in the United States. Given that perchlorate inhibits thyroidal iodine transport and therefore has antithyroid properties, ingestion of water containing perchlorate could cause hypothyroidism. This cohort study was undertaken to determine the frequency of hypothyroidism and other thyroid disorders in people consuming water with varying perchlorate concentrations.

Methods The cohort consisted of all 176,847 Medicaid recipients living in Nevada in 1997 and 1998. The frequency of physician diagnoses of hypothyroidism, goiter, thyroid nodular disease, and other thyroid disorders in this cohort was determined from claims data during this time period and then linked to the county of residence. Perchlorate was measured repeatedly in water samples collected in all counties of the state during the 2-year period and the results averaged. No information concerning the basis for any of the thyroid diagnoses is provided, and all personal identifiers were removed from the database, and therefore the sex and age of the subjects with thyroid disease is not known.

Results The perchlorate concentrations in Clark County, Nevada, averaged 8 µg/L (range, 4.1 to 14.0) in 1997 and 1998. This county includes Las Vegas, and is the most populous county in the state. Perchlorate was not detected (<4 µg/L) in the water at any time in Washoe County, which includes Reno, or any other county in the state. There were no differences in the prevalence of the different thyroid disorders in the subjects residing in Clark County and either Washoe County or any of the other counties in which no perchlorate was detectable (table, data for thyroiditis and other disorders not shown).

Table. Thyroid Disorders in Residents of Different Counties in Nevada, 1997-1998.

County	No.*	Acquired Hypothyroidism		Congenital Hypothyroidism		Goiter		Nodular Goiter		Hyperthyroidism		Cancer	
		No.	%	No.	%	No.	%	No	%	No.	%	No.	%
Clark	122,519	1445	1.18	15	0.01	139	0.11	114	0.09	300	0.24	28	0.02
Washoe	29,622	346	1.17	6	0.02	27	0.09	19	0.06	71	0.24	9	0.03
Other	24,706	355	1.44	1	0.00	26	0.11	24	0.10	76	0.30	7	0.03
Total	176,847	2146	1.21	22	0.01	192	0.11	157	0.09	447	0.25	44	0.02

Assuming that the subjects ingested 2 liters of water daily, their perchlorate intake would be approximately 16 µg daily, much less than the minimum amount needed to inhibit thyroid iodine uptake.

Conclusion Environmental contamination of public water supplies in Nevada is not associated with any thyroid disorder, including congenital hypothyroidism.

COMMENTARY

The water in Clark County, Nevada, and in Arizona and Southern California comes from Lake Mead or the Colorado River below the lake. This lake has been contaminated with perchlorate as a result of spillage of ammonium perchlorate from production sites (now closed) on tributaries draining into the lake or the river above it. This study indicates that the amount of perchlorate is too small to cause hypothyroidism, and there is no reason to suspect that it might cause any other thyroid disease. The possibility that the frequency of congenital hypothyroidism is increased in areas where the water contaminated with perchlorate has been studied several times, mostly with negative results. However, in one study the median serum thyrotropin (TSH) value was higher in exposed than unexposed infants (19.9 vs. 13.4 mU/L), but the exposed infants were tested sooner after birth than the unexposed infants. Cross-sectional surveys of perchlorate workers in Nevada and Utah, in whom the exposure, by inhalation, was approximately 30 mg daily, revealed no abnormalities in thyroid function (1).

In normal subjects, oral administration of 10 mg of potassium perchlorate daily for two weeks has no effect on serum thyroid hormone and TSH concentrations, but lowers thyroid iodine-123 uptake by approximately 40 percent (2). If it persisted, such a reduction in iodine uptake might cause hypothyroidism, but the studies of occupational exposure suggest otherwise. In doses of 400 to 1000 mg daily, perchlorate definitely has antithyroid properties, and it seems to be safe as long as it is not given for a prolonged period (1).

Robert D. Utiger, M.D.

References

1. Soldin OP, Braverman LE, Lamm SH. Perchlorate clinical pharmacology and human health: a review. Ther Drug Monit 2001;23:316-31.

2. Lawrence JE, Lamm SH, Pino S, et al. The effect of short-term low-dose perchlorate on various aspects of thyroid function. Thyroid 2000;10:659-63.

Triiodothyronine stimulates thermogenesis by promoting uncoupling of mitochondrial energy production and utilization

Lebon V, Dufour S, Petersen KF, Ren J, Jucker BM, Slezak LA, Cline GW, Rothman DL, Shulman GI. Effect of triiodothyronine on mitochondrial energy coupling in human skeletal muscle. J Clin Invest 2001;108:733-7.

SUMMARY

Background The utilization of substrate via the tricarboxylic acid cycle is normally closely coupled to the electron transport chain, oxygen consumption, and synthesis and utilization of ATP. Hydrogen ions produced by substrate metabolism are pumped from within mitochondria into the space between the inner and outer mitochondrial membranes and then are taken up by mitochondria for use during ATP synthesis. The close linkage between the formation and utilization of hydrogen ions is interrupted if hydrogen ions flow back into mitochondria through another pathway, bypassing the ATP synthetic pathway. When this occurs, heat is generated and more substrate must be used to provide sufficient hydrogen ions to maintain ATP synthesis; substrate utilization is said to be uncoupled from ATP synthesis.

Thyroid hormone increases substrate utilization, oxygen consumption, and thermogenesis. In vitro studies suggested that it might uncouple substrate utilization from the synthesis of ATP, but high doses of hormone were required and in vivo evidence was lacking. This study was undertaken to determine if thyroid hormone stimulates uncoupling in vivo.

Methods Tricarboxylic acid cycle activity and ATP synthesis in skeletal muscle were measured by carbon-13 (C-13) and phosphorus-31 (P-31) nuclear magnetic resonance spectroscopy in 7 normal subjects (mean age, 25 years) after an overnight fast before and after administration of triiodothyronine (T_3) in a dose of 100 μg twice daily for three days. Tricarboxylic acid cycle activity was determined by measuring the conversion of C-13-acetate into C-13-glutamic acid and ATP synthesis by measuring the rate of conversion of inorganic P-31 to P-31-ATP.

Results Administration of T_3 for three days resulted in a mean weight loss of 1 kg, an increase in heart rate of 19 beats/min, and an increase in whole-body oxygen consumption of 17 percent. The mean serum T_3 concentration was 93 ng/dL (1.4 nmol/L) at base line, and it was 552 ng/dL (8.5 nmol/L) 12 hours after the last dose of T_3. The mean rate of tricarboxylic acid cycle activity increased by 70 percent (0.064 to 0.109 mmol/g/min, P=0.01). In contrast, the rate of synthesis of ATP did not change significantly (5.2 to 4.6 mmol/g/min, P=0.16). The ratio of ATP synthesis to tricarboxylic acid cycle activity decreased by 45 percent (P<0.01), indicating substantial uncoupling of energy production and utilization in mitochondria.

Conclusion In normal subjects, administration of high doses of T_3 for three days stimulates substrate utilization but not ATP synthesis in muscle, thereby reducing mitochondrial energy coupling.

COMMENTARY

That thyroid hormone stimulates basal substrate utilization and oxygen consumption has long been known, but the mechanisms by which the stimulation occurs are controversial. Proposed mechanisms include increased rates of synthesis of protein, ion transport across cell membranes, and substrate cycling, all of which require ATP synthesis, and uncoupling of substrate utilization from ATP synthesis, which would reduce the efficiency and possibly the magnitude of ATP synthesis.

This study provides in vivo evidence that uncoupling does indeed occur in hyperthyroidism. Notwithstanding the short duration and severity of the induced hyperthyroidism, it seems very likely that the results apply to patients with chronic and less severe hyperthyroidism. (With regard to the severity of hyperthyroidism, the post-T_3 value of 552 ng/dL (8.5 nmol/L) would likely have been the nadir value between doses.) The contribution of this and other mechanisms of increased oxygen consumption to the overall increase in oxygen consumption may well vary with the duration and severity of hyperthyroidism, depending, for example, on the speed of onset and the extent of stimulation of other metabolic reactions.

How might thyroid hormone cause uncoupling of substrate utilization and ATP synthesis? One possibility is an increase in the activity of mitochondrial uncoupling protein. These proteins, which are located on the inner membrane of mitochondria, catalyze the transfer of hydrogen ions into mitochondria, where they are converted to heat, so that fewer of the ions are available for ATP synthesis. Among the three known uncoupling proteins (UCP-1, UCP-2, and UCP-3), UCP-3 is found mostly in muscle, in which it is the predominant form (1). The levels of UCP-3 mRNA, and presumably UCP-3 protein and therefore UCP-3 activity, in skeletal muscle are increased by daily administration of 75 to 100 μg T_3 to humans for 14 days and also by incubation of human skeletal muscle cells with T_3 in vitro (2), providing a plausible although unproven explanation for the uncoupling described by Lebon et al.

Robert D. Utiger, M.D.

References

1. Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. Nature 2000;404:652-60.

2. Barbe P, Larrouy D, Boulanger C, et al. Triiodothyronine-mediated up-regulation of UCP2 and UCP3 mRNA expression in human skeletal muscle without coordinated induction of mitochondrial respiratory chain genes. FASEB J 2001; 15:13-5.

Thyroid Review Articles

Cooper DS. Subclinical hypothyroidism. N Engl J Med 2001;345:260-5.

Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy: use of a detailed protocol with comparative photographs for objective assessment. Clin Endocrinol 2001;55:283-303.

Gillam M, Kopp P. Genetic regulation of thyroid development. Curr Opin Pediatr 2001;13:358-63.

Gillam M, Kopp P. Genetic defects in thyroid hormone synthesis. Curr Opin Pediatr 2001;13:364-72.

Henneman G, Docter R, Friesema ECH, et al. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev 2001;22:451-76.

Krohn K, Paschke R. Progress in understanding the etiology of thyroid autonomy. J Clin Endocrinol Metab 2001;86:3336-45.

Rapaport R, Rose SR, Freemark M. Hypothyroxinemia in the preterm infant: the benefits and risks of thyroxine treatment. J Pediatr 2001;139:182-8.

Toft AD. Subclinical hyperthyroidism. N Engl J Med 2001;345:512-6.