CLINICAL THYROIDOLOGY

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Five Years, and a Questionnaire

This issue marks the end of the fifth year of Clinical Thyroidology as a publication of the American Thyroid Association and of my fifth year as editor.

There have been 15 issues, each, like this, containing summaries of and commentary about 20 recently published original scientific articles—certainly the core of the journal—and a listing of recently published review articles and an occasional editorial. The original articles chosen have always been published in the preceding few months and have covered all aspects of thyroid physiology and disease. In searching for articles to include, I have looked hard for articles published in journals that I think are less likely to be read by the average reader than are general medical journals or journals of clinical endocrinology. But I don't really know who the average reader is. I know the mailing list includes the members of the American Thyroid Association, but their number is far less than the total list (now more than 12,000 names long). I have worried about missing articles that should be brought to readers' attention. And I have held firmly to the policy of limiting each summary and commentary to a single page; it forces me to write concise summaries and limits the amount of pontificating in the commentary, whether written by a colleague or myself. I have had no financial relationships with or indeed any communication from Monarch Pharmaceuticals, which provides a grant to the association to support the journal.

For the future, I do not plan to change the basic policies and procedures described above. I will continue to worry about missing important articles, balance, and timeliness of publication, both of the articles selected for inclusion and the journal itself. Are there other things I should be worrying about? One aspect of the journal will change, and that will be to make it more of an on-line journal. Currently, there are identical print and on-line versions (at www.thyroid.org), and both are available to all subscribers. Shortly, we plan to ask international readers to become on-line readers, and will notify them when each issue becomes available.

One hope I have for the future is to hear more from you—the readers. Have important articles been missed? Have there been too many articles on some topics, or not enough on others? Has there been too much opinion, or too little? At the bottom of the page you will find a very short questionnaire, which I hope you will complete and return to me.

In my first issue (March, 2001), I said I thought editing Clinical Thyroidology "will be fun, informative and stimulating". It has been all of the above, and I am sure will continue to be for me. I hope it is informative and stimulating for you as well.

Robert D. Utiger, M.D.

Questions for Readers

Please return by mail, fax, or e-mail (see upper left corner of this page for addresses).

1. The journal should contain more articles about the following topics.
2. The journal should contain fewer articles about the following topics.
3. In the one article per page format, should summaries or commentaries be longer?
4. Should the format be changed, so that more space is devoted to each article?
5. My specialty or main area of interest is?
6. Other comments.

Thank you.

Serum thyrotropin values are similar in healthy subjects and healthy subjects with no risk factors for thyroid disorders

Kratzsch J, Fiedler GM, Leichtle A, Brugel M, Buchbinder S, Otto L, Sabri O, Matthes G, Thiery J. New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem 2005;51:1480-6.

SUMMARY

Background Thyroid disorders are rather common in the general population, and therefore healthy people with these disorders may have been included in the groups in which reference ranges for serum thyrotropin (TSH), thyroid hormones, and antithyroid antibodies were determined. In this study serum TSH, thyroxine (T_4), free T_4, triiodothyronine (T_3), free T_3, and antithyroid peroxidase (TPO) and antithyroglobulin (Tg) antibodies were measured in a large group of blood donors and a subgroup formed by exclusion of people who might have thyroid disorders.

Methods The study was done in Leipzig, Germany. The first study group (complete group) consisted of 870 blood donors (425 women, 445 men; mean age, 33 years); 34 were aged 18 to 19.9 years, 382 were 20 to 29.0 years, 174 were 30 to 39.9 years, 172 were 40 to 49.9 years, 70 were 50 to 59.9 years, and 37 were ≥60 years. Among these subjects, 220 (25 percent) were excluded on the basis of a family history of thyroid disorders or abnormal thyroid ultrasonography; 26 percent of the women and 16 percent of the men had a positive family history, and 27 percent of the women and 24 percent of the men had an enlarged thyroid (volume >18 ml in women and >25 ml in men) or one or more thyroid nodules. An additional 197 subjects (23 percent) were excluded because they had a high serum anti-TPO or anti-Tg antibody concentration. Thus, the second study group (constraint group) consisted of 443 subjects (174 women, 279 men; mean age 32 years, with an age distribution similar to that of the complete group).

Serum TSH, thyroid hormones, and thyroid antibodies were measured by immunometric assays. The reference group for serum anti-TPO and anti-Tg values consisted of 130 nonsmoking men ≤50 years old with no family history of thyroid disease, no abnormalities on ultrasonography, and serum TSH concentrations between 0.5 and 2.0 mU/L. The respective upper reference intervals (97.5th percentile) were 37 U/ml and 98 U/ml.

Results The results of the measurements of serum TSH and thyroid hormones in the complete group and the constraint group were similar, except that the calculated lower limit for serum TSH (2.5th percentile) was lower in the complete group (Table).

Table. Median (2.5th to 97.5th Percentile) Values for Serum TSH and Thyroid Hormone Concentrations in the Complete (n=870) and Constraint Groups (n=453).

	Complete Group	Constraint Group
Serum TSH (mU/L)	1.31 (0.30-3.63)	1.36 (0.40-3.77)
Serum T_4 (μg/dl)	7.8 (5.5-12.2)	7.6 (5.5-12.2)
Serum free T_4 (ng/dl)	1.25 (0.98-1.61)	1.25 (0.99-1.58)
Serum T_3 (ng/dl)	115 (80-182)	115 (82-181)
Serum free T_3 (ng/dl)	0.33 (0.25-0.43)	0.33 (0.26-0.44)

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

The serum TSH and thyroid hormone values were not normally or log-normally distributed. Stepwise regression analyses revealed age to be the only independent predictor of serum TSH; serum TSH values were higher in subjects aged <40 years than older subjects (median, 1.46 vs. 1.14 mU/L; 2.5th to 97.5th percentiles, 0.5 to 3.5 vs. 0.3 to 3.9 mU/L).

Conclusion Serum TSH and thyroid hormone concentrations are very similar in healthy subjects and the subset of healthy subjects who have no family history of thyroid disease, no thyroid enlargement or thyroid nodules, and normal serum antithyroid antibody concentrations.

COMMENTARY

Various organizations and people have proposed that the reference limits for TSH be narrowed from, for example, 0.5 to 4.0 mU/L to 0.4 to 2.5 mU/L, or thereabouts. The primary basis for this proposal is that population mean or median values are often 1.4 to 1.8 mU/L, not in the middle of the normal range, and therefore people with values of, for example, 3.2 or 3.8 mU/L, must have thyroid disease. They are people who tend to have some of the three factors listed in the Summary, further evidence that they have thyroid disease and should not be considered normal.

The results of this study indicate that subjects without these factors have serum TSH values that are little different from the larger group that includes subjects who do have the factors. To be sure, the reference ranges for both groups were a little narrower than those specified by many laboratories, possibly because even the complete group was more carefully selected than usual. How much of this difference is analytical (assay-dependent) and how much is biologic variation (would the values be the same in people of different race/ethnicity or those who live an another country?) is uncertain.

What the results certainly do suggest is that arbitrary change in the reference range is inappropriate. Even if the reference value were to change on the basis of sound biologic data, it is extremely unlikely that anyone with a serum TSH value of, for example, 3.9 mU/L, would benefit from T_4 therapy or even close follow up.

Robert D. Utiger, M.D.

Both day- and night-time heart rate and systolic blood pressure are high in patients with hyperthyroidism

Iglesias P, Acosta M, Sanchez R, Fernandez-Reyes MJ, Mon C, Diez JJ. Ambulatory blood pressure monitoring in patients with hyperthyroidism before and after control of thyroid function. Clin Endocrinol (Oxf) 2005;63:66-72.

SUMMARY

Background Hyperthyroidism causes many changes in cardiovascular function, prominent among them being an increase in cardiac rate and contractility and a decrease in systemic vascular resistance. These changes typically result in tachycardia and systolic hypertension, but the extent to which heart rate and blood pressure are altered around the clock is uncertain. In this study, heart rate and blood pressure were continuously monitored for 24 hours in patients with hyperthyroidism before and after antithyroid treatment and normal subjects.

Methods The study subjects were 20 patients (18 women, 2 men; mean age, 49 years) with hyperthyroidism caused by Graves' disease (19 patients) or nodular goiter (1 patient) and normal blood pressure (<140/90 mm Hg). All had high serum free thyroxine (T_4) and low serum thyrotropin (TSH) concentrations. Their mean body-mass index was 22.4 kg/m^2, and at the clinic their mean heart rate was 92 beats/min and their mean blood pressure was 130/76 mm Hg. Heart rate and blood pressure were measured at 30-minute intervals during the day (10 am to 10 pm) and at 60-minute intervals during the night (10 pm to 10 am) using an oscillatory ambulatory monitor. The 24-hour monitoring was repeated in 18 patients 12 months later when they were euthyroid (most were treated with an antithyroid drug). In addition, 15 normal subjects (14 women, 1 man; mean age, 47 years) were studied once.

Results The mean 24-hour heart rate was higher in the patients with hyperthyroidism than in the normal subjects (88 vs. 72 beats/min), as was the mean 24-hour systolic blood pressure (125 vs. 115 mm Hg), but their diastolic blood pressure was similar (71 vs. 69 mm Hg). The day- and night-time heart rate and systolic blood pressure also were higher in the patients, but there were no differences in the diastolic blood pressure or the percentage fall in either heart rate or systolic blood pressure at night in the two groups.

The patients' mean 24-hour heart rate and systolic blood pressure, but not diastolic blood pressure, were lower after antithyroid treatment than at base line (Table). Both the day- and night-time heart rates were lower after treatment, but systolic blood pressure was lower only during the day.

Table. Results of 24-Hour Ambulatory Monitoring of Heart Rate and Blood Pressure in 18 Patients with Hyperthyroidism before and after Antithyroid Treatment.

	Base Line	After Treatment
Heart rate (beats/min)	87	72*
Systolic blood pressure (mm Hg)	126	120*
Diastolic blood pressure (mm Hg)	71	72

*P<0.05, as compared with base line.

There was no correlation between the serum free T_4 concentrations and heart rate or blood pressure either before or after antithyroid therapy.

Conclusion Patients with hyperthyroidism have a rapid heart rate and high systolic blood pressure, but not diastolic blood pressure, during both day and night, and the changes are reversible with antithyroid treatment.

COMMENTARY

These results demonstrate that a higher systolic blood pressure in patients with hyperthyroidism is not simply a "white-coat" finding, but is continuously present. There was a circadian variation in not only heart rate but also systolic blood pressure, and systolic blood pressure was higher in the patients than in the normal subjects during both day and night. The presence of day–night variation in the patients and the similar magnitude of that variation in the patients and normal subjects indicate that the circadian control of blood pressure is not altered by hyperthyroidism. The causes of the increase in systolic blood pressure are an increase in cardiac output and a decrease in arterial compliance. At the same time, systemic vascular resistance is decreased, and therefore diastolic blood pressure is not increased. These changes are reversible with antithyroid therapy.

Isolated systolic hypertension is a well-recognized entity, especially in elderly patients, and such patients should be screened for thyroid dysfunction. How often it occurs in patients with hyperthyroidism and, more important, how often it contributes the morbidity of hyperthyroidism, are not known. In the absence of ischemic heart disease or cardiac failure, antihypertensive therapy is not indicated. A β-adrenergic antagonist drug will usually rapidly lower heart rate and systolic blood pressure, and may raise diastolic pressure as well.

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Subclinical hyperthyroidism may remit spontaneously

Woeber KA. Observations concerning the natural history of subclinical hyperthyroidism. Thyroid 2005;15:687-91.

SUMMARY

Background Subclinical hyperthyroidism, defined as a low serum thyrotropin (TSH) and a normal serum free thyroxine (T_4) concentration, has been found in 1 to 3 percent of people in cross-sectional surveys of thyroid function. Two important causes of subclinical hyperthyroidism are Graves' disease and multinodular goiter. The natural history of subclinical hyperthyroidism, in particular the likelihood of progression to overt hyperthyroidism, caused by these two disorders is not known. In this study, small groups of patients with these disorders were followed to determine the risk of progression.

Methods The study subjects were 16 patients with subclinical hyperthyroidism referred to an endocrine practice. None had any history of thyroid disease, was taking any drug that alters thyroid function, or had any clinical manifestations of hyperthyroidism.

Seven patients (5 women, 2 men; age range, 35 to 82 years) had Graves' disease, as defined by a high serum concentration of thyrotropin (TSH)-receptor antibodies (TSH-RAb). One had mild Graves' ophthalmopathy and four had a goiter. Nine patients (7 women, 2 men; age range, 34 to 74 years) had a multinodular goiter, confirmed by ultrasonography. None of these patients had a high serum TSH-RAb concentration.

The patients were reevaluated at varying intervals, at which times serum TSH, free thyroxine (T_4), free triiodothyronine (T_3), and TSH-RAb were measured.

Results The seven patients with subclinical hyperthyroidism caused by Graves' disease were followed for 14 to 36 months. Serum TSH concentrations increased to normal in five in 3 to 19 months, and serum TSH-RAb values decreased to normal or near-normal in four of them, with little change in serum free T_4 and free T_3 concentrations (Table). One patient followed for 15 months had persistent subclinical hyperthyroidism. One patient had a normal serum TSH concentration (0.46 mU/L) at 9 months, but had overt hyperthyroidism at 36 months.

Table. Initial and Final Serum TSH, Free T_4, Free T_3, and TSH-RAb Concentrations in Patients with Subclinical Hyperthyroidism Caused by Graves' Disease or Multinodular Goiter.

	Serum TSH (mU/L)	Serum Free T_4 (ng/dl)	Serum Free T_3 (ng/dl)	Serum TSH-RAb (%)
	Graves' Disease (n=7)			
Initial values	<0.03-0.13	0.8-1.6	0.3-0.4	138-284
Final values	<0.03-1.95	0.9-1.9	0.3-0.5	102-175
	Multinodular Goiter (n=9)			
Initial values	0.05-0.25	0.9-1.4	0.2-0.3	
Final values	0.03-0.37	0.9-1.4	0.3-0.4	

Normal values: TSH, 0.5-4.7 mU/L; free T_4, 0.7-1.9 ng/dl; free T_3, 0.2-0.4 ng/dl, TSH-RAb, <125%. To convert free T_4 and free T_3 to pmol/L, multiply by 12.9 and 15.4, respectively.

There was no change in thyroid function in the 9 patients with a multinodular goiter during a follow-up period of from 11 to 36 months (Table), but one patient had some symptoms of hyperthyroidism after 11 months and was treated with methimazole.

Conclusion Subclinical hyperthyroidism caused by Graves' disease may remit spontaneously or persist for a prolonged period, whereas when caused by a multinodular goiter it is usually persistent.

COMMENTARY

Graves' disease and multinodular goiter are common causes of subclinical hyperthyroidism, but their relative frequency and that of other causes, such as silent (painless) thyroiditis, have not been studied often. In one study of 50 patients, all of whom had thyroid radioiodine uptake and imaging studies, 25 (50 percent) had a multinodular goiter, 9 (18 percent) had Graves' disease, 4 (8 percent) had a hyperfunctioning thyroid adenoma, and 1 (2 percent) had silent thyroiditis, but 11 (22 percent) were not given a causal diagnosis (1).

The results of such studies obviously depend on not only the diligence with which the patients are studied, but also how long they are followed. It should not be difficult to identify the cause if it is a multinodular goiter, but to identify the cause if it is Graves' disease is more difficult. That is because it doesn't take much TSH-RAb to raise serum thyroid hormone concentrations enough to inhibit TSH secretion, and that amount of TSH-RAb may not be detected in any of the serum assays for these antibodies.

The cause of subclinical hyperthyroidism can usually be determined by history, palpation of the thyroid gland, and observation for a month or two. The results of imaging studies and measurements of TSH-RAb in serum may ease uncertainty about the diagnosis, but are not essential. The important issues are the patient's vulnerability to a little thyroid hormone excess and the likelihood of either remission or progression to overt hyperthyroidism. What this study revealed is that subclinical hyperthyroidism caused by Graves' disease often goes away, whereas subclinical hyperthyroidism caused by a multinodular goiter is unlikely to go away.

Robert D. Utiger, M.D.

Reference

1. Tollin SR, Fallon EF, Mikhail M, et al. The utility of thyroid nuclear imaging and other studies in the detection and treatment of underlying thyroid abnormalities in patients with endogenous subclinical thyrotoxicosis. Clin Nucl Med 2000;5:341-7.

Concomitant glucocorticoid therapy does not alter the efficacy of radioiodine therapy in patients with hyperthyroidism caused by Graves' disease

Jensen BE, Bonnema SJ, Hegedus L. Glucocorticoids do not influence the effect of radioiodine therapy in Graves' disease. Eur J Endocrinol 2005;153:15-21.

SUMMARY

Background Patients with hyperthyroidism caused by Graves' disease who are treated with radioiodine (I-131) are more likely to have the onset or worsening of ophthalmopathy than are those treated with an antithyroid drug. Concomitant glucocorticoid therapy reduces the likelihood of changes in the eyes. Whether it alters the antithyroid effect of I-131 therapy was evaluated in this study.

Methods The effect of a first dose of I-131 with or without glucocorticoid therapy on thyroid function was studied in 207 patients with hyperthyroidism caused by Graves' disease. Ninety-six patients (82 women, 14 men; mean age, 45 years) were treated with I-131 plus 25 mg of prednisolone daily for 30 days, starting two days before I-131 was given, and 111 (86 women, 25 men; mean age, 51 years) were treated with I-131 alone. The indications for the addition of prednisolone were mild-to-moderate Graves' ophthalmopathy in 56 patients, smoking in combination with high serum concentrations of thyrotropin (TSH)-receptor antibodies in 32, and both in 8. No patient in the I-131 group had ophthalmopathy, but 46 were smokers. Approximately 50 percent of the patients in each group had recurrent hyperthyroidism after prolonged antithyroid drug therapy. Most patients were treated with an antithyroid drug until four days before I-131 was given.

The patients were evaluated at 3, 6, and 12 weeks and then at 3-month intervals for 1 year after I-131 therapy. Patients who had persistent hyperthyroidism were given a second dose of I-131 9 or more months after the first treatment. Hypothyroidism was confirmed as persistent by cessation of thyroxine (T_4) therapy. The patients were classified as euthyroid, hypothyroid, or hyperthyroid (the latter including those patients given a second dose of I-131) according to their status one year after I-131 therapy.

Results The mean pretreatment thyroid volume, serum thyroid hormone and TSH-receptor antibody values, and 24-hour thyroid I-131 values were similar in the I-131 plus prednisolone group and the I-131 group. The mean I-131 dose was 10 mCi (373 MBq) in both groups.

The frequency of normal thyroid function, hypothyroidism, and hyperthyroidism one year after I-131 therapy was similar in the I-131 plus prednisolone group and the I-131 group (Table). Younger patients and those with a smaller thyroid gland were more likely to be euthyroid or hypothyroid, but prednisolone treatment and smoking status were not related to outcome.

Table. Outcome of I-131 Therapy at One Year in the I-131 plus Prednisolone Group and the I-131 Group.

	I-131 plus Prednisolone (n=96)	I-131 (n=111)
Hypothyroid	36%	35%
Euthyroid	25%	24%
Hyperthyroid	39%	41%

Among the patients in the I-131 plus prednisolone group, 55 (57 percent) had no change in their eyes, preexisting ophthalmopathy improved in 34 (36 percent), and 7 (7 percent) had the onset or worsening of ophthalmopathy during the 1-year follow-up period. Four patients (4 percent) in the I-131 group had onset of ophthalmopathy during follow-up.

Conclusion In patients with hyperthyroidism caused by Graves' disease, administration of prednisolone for 30 days starting when I-131 is given does not alter the long-term effect of I-131 therapy.

COMMENTARY

Would the results have been different if, for example, most if not all of the patients had not been previously treated with an antithyroid drug? Probably not. Most of the patients were given methimazole, and it does not alter the efficacy of I-131 (1). What if the doses of I-131 had been higher, and hence caused more cellular injury and inflammation and release of more thyroid antigens, which might have been prevented by the prednisolone? The doses of I-131 were relatively low, as judged by both the actual doses given and the rather high frequency of persistent hyperthyroidism. Still, it seems unlikely that prednisolone would have had an effect had the I-131 dose been higher. Finally, would the results have been different if the characteristics of the patients in the two groups were similar? That also seems unlikely. While the groups were different with respect to risk of onset or worsening of ophthalmopathy, they were similar with respect to thyroid size, thyroid function, serum TSH-receptor antibody concentrations, and I-131 doses, and it is these characteristics that most likely determine the effect of I-131 therapy on the thyroid.

Robert D. Utiger, M.D.

Reference

1. 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.

Mortality is slightly increased after radioiodine therapy in patients with hyperthyroidism

Franklyn JA, Sheppard MC, Maisonneuve P. Thyroid function and mortality in patients treated for hyperthyroidism. JAMA 2005;294:71-80.

SUMMARY

Background Mortality may be increased in patients with hyperthyroidism, including those who have been treated. Among the latter, however, the role of persistent hyperthyroidism or hypothyroidism is uncertain. In this study the mortality of patients with hyperthyroidism who had been treated with radioiodine (I-131) was determined.

Methods The study subjects were 2668 patients aged 40 years or older with hyperthyroidism treated with I-131 between 1984 and 2002. Serum free thyroxine (T_4) and thyrotropin (TSH) were measured annually starting about one year after the patients had become euthyroid. Patients in whom overt hypothyroidism developed during follow-up were treated with T_4, but those with subclinical hypothyroidism or subclinical hyperthyroidism were not treated. The status of these 2668 patients was determined in December, 2003 by a search of the United Kingdom national mortality data base. The death certificates of those who had died were reviewed, and the results were compared with those of all patients of the same age and sex who died in the same year in England and Wales. The person-years at risk was defined as the period from first serum TSH measurement after the patient became euthyroid to death or December 2003.

Results Among the 2668 patients, there were 2163 women (81 percent) and 505 men (19 percent). Their median age at the time of first serum TSH measurement was 62 years. They had been treated with 5 or 10 mCi (185 or 370 MBq) of I-131; 417 (16 percent) had received two or more doses. At death or study end, 1212 patients (45 percent) were being treated with T_4.

There were 554 deaths during a median follow-up period of 5.6 years (15,968 person-years at risk), whereas 487 were expected (standardized mortality ratio [SMR], 1.14; 95 percent confidence interval, 1.04 to 1.24). There were increases in death from cardiovascular diseases, specifically the subgroup that includes cardiac failure and arrhythmias, in women; respiratory diseases in men; and endocrine and metabolic disease in women and men combined.

All-cause and cardiovascular-disease mortality rates were higher in patients who were never treated with T_4 or before T_4 was given (SMR, 1.26), but not in those treated with T_4 (SMR given only if confidence interval excluded 1.00). Among the patients who were treated with T_4, the all-cause and cardiovascular-disease mortality rates were significantly lower than in those not treated with T_4 (hazard ratio for both comparisons, 0.65).

In patients not receiving T_4, the all-cause mortality rates were increased in those with low serum TSH values (<0.5 mU/L) (SMR, 1.19) and in those with normal serum TSH values (0.5 to 5.0 mU/L) (SMR, 1.40), but not in those with high serum TSH values (>5.0 mU/L). The SMR for cardiovascular-disease mortality was high (SMR, 1.53) only in the patients with normal serum TSH values.

Among the same patients (never treated or before treatment), the all-cause and cardiovascular-disease mortality rates during follow-up were similar in the patients with normal serum TSH values and in those with low or high serum TSH values when first measured. There also were no differences in all-cause or cardiovascular-disease mortality rates in patients with repeated serum TSH values that were low, normal, or high.

Conclusion All-cause and cardiovascular-disease mortality is increased in patients with hyperthyroidism after I-131 therapy, but not in those who have overt hypothyroidism and are treated with T_4.

COMMENTARY

These patients were treated with rather low doses of radioiodine, but one dose was said to be effective in 84 percent, and only 45 percent later had overt hypothyroidism. It is important to note that serum TSH was first measured and follow-up began more than a year after the patients had become euthyroid, and some were already taking T_4 at that time. The first serum TSH value was low in 1168 (44 percent), normal in 1025 (38 percent), and high in 472 (18 percent). The numbers of patients in most other subgroups groups were not given.

There are really two sets of data here. One concerns the entire cohort and subdivision of it into those patients who had overt hypothyroidism and were treated with T_4 (how well was not stated) and all others, and the other concerns subdivision of the cohort according to their serum TSH values. The higher mortality rate in the entire cohort was primarily due to death from those cardiovascular disorders often associated with hyperthyroidism (heart failure, arrhythmias) in the patients not taking T_4. The higher mortality in this group cannot be attributed to subclinical hyperthyroidism, but could reflect ongoing deleterious effects of the preceding hyperthyroidism. The lower mortality rate in the T_4-treated group led the authors to suggest that the goal of I-131 therapy should be overt hypothyroidism, which is then treated. That is already achieved in most patients in the United States, and given the concerns about T_4 over- and under-treatment the good outcome in this group is reassuring.

Robert D. Utiger, M.D.

Radioiodine therapy for hyperthyroidism is not followed by exacerbation of eye disease in patients with mild Graves' ophthalmopathy

Perros P, Kendall-Taylor P, Neoh C, Frewin S, Dickinson J. A prospective study of the effects of radioiodine therapy for hyperthyroidism in patients with minimally active Graves' ophthalmopathy. J Clin Endocrinol Metab 2005;90:5321-3.

SUMMARY

Background Patients with Graves' disease may have the onset of ophthalmopathy before, at the time of, or after the onset of hyperthyroidism, and it may worsen after the initiation of antithyroid therapy, in particular, radioactive iodine (I-131) therapy. This study was performed to determine the effect of I-131 therapy in patients with minimally active ophthalmopathy.

Methods The study subjects were 72 patients (50 women, 22 men; median age, 52 years) with minimally active Graves' ophthalmopathy, as defined by absence of chemosis, Clinical Activity Score ≤3 (presence [1 point] or absence [0 point] of orbital pain at rest or with motion; swelling of the conjunctiva, cornea, or caruncle; and erythema of the conjunctiva or eyelids [maximum possible score, 7]), and no increase in eye symptoms in the preceding 2 or 3 months. The patients had 20±3 mm (mean ±SD) of proptosis, and 24 (33 percent) had some diplopia. Forty-one (57 percent) had a history of moderate- to-severe ophthalmopathy, including optic neuropathy in 10. The median duration of ophthalmopathy was 24 months (range, 2 to 360). The median duration of hyperthyroidism was 18 months (range, 0 to 132); 60 patients had been taking an antithyroid drug and thyroxine (T_4) and 9 an antithyroid drug alone. Most were clinically and biochemically euthyroid when treated with I-131.

Therapy was stopped, and I-131 (mean dose, 11 mCi [405 MBq]) was given 1 to 2 weeks later. Two weeks after that, T_4 was started in a dose of 50 μg or higher depending on the patient's preceding T_4 and antithyroid drug doses. The patients were examined by an ophthalmologist at base line and at 2, 4, 6, and 12 months after I-131 therapy. Serum thyrotropin (TSH) and free T_4 were measured at these times, and the T_4 dose was adjusted as needed to avoid high serum TSH values and low or high serum free T_4 values.

Results After I-131 therapy, there was a small progressive decrease in both the Clinical Activity Score and proptosis (Table 1), and also small decreases in the width of the palpebral opening, soft tissue swelling, and diplopia. No patient had worsening of ophthalmopathy.

Table 1. Changes in Mean Clinical Activity Score and Proptosis after I-131 Therapy.

	Clinical Activity Score	Proptosis (mm)
Before I-131 therapy	0.8	19.6
2 months	0.7	19.4
4 months	0.5	19.4
6 months	0.4	19.2
12 months	0.4	19.2

At the time antithyroid drug and T_4 therapy was stopped before I-131 therapy, and at all times thereafter, approximately 40 percent of the patients had subclinical hyperthyroidism, and other types of thyroid dysfunction occurred as well (Table 2). The dose of T_4 was altered in approximately 20 percent of patients at each of the time intervals shown, and in 5 patients with overt hyperthyroidism T_4 was stopped and antithyroid drug therapy was resumed 2 to 6 months after I-131 therapy. The median dose of T_4 at 12 months was 125 μg daily.

Table 2. Thyroid Function before and after I-131 Therapy.

	Hypothyroidism		Hyperthyroidism	
	Subclinical	Overt	Subclinical	Overt
Before I-131 therapy	0%	2%	41%	7%
2 months	9%	6%	42%	18%
4 months	24%	2%	40%	6%
6 months	12%	4%	41%	6%
12 months	9%	2%	46%	0%

Conclusion Among patients with mild, minimally active ophthalmopathy and hyperthyroidism caused by Graves' disease, I-131 therapy for hyperthyroidism does not result in exacerbation of ophthalmopathy.

COMMENTARY

In this study I-131 therapy was followed by mild improvement in ophthalmopathy in some patients, and worsening in none. The patients had not only minimally active, but also stable ophthalmopathy. Most had been treated for hyperthyroidism for many months, during which time previously active ophthalmopathy, present earlier in a substantial proportion (57 percent), must have subsided. They were, therefore, not comparable with the patients with newly diagnosed hyperthyroidism in the randomized trials in which I-131-treated patients were somewhat more likely to have the onset or progression of ophthalmopathy than patients treated with an antithyroid drug or thyroidectomy.

The protocol for this study was designed to prevent hypothyroidism after I-131 therapy, because of evidence that its occurrence at this time may exacerbate ophthalmopathy. Preventing hypothyroidism is a worthwhile goal in any patient treated with I-131, but whether that contributed to the mild improvement in ophthalmopathy in these patients is far from clear.

Robert D. Utiger, M.D.

Intravenous glucocorticoid therapy is more effective than oral glucocorticoid therapy in patients with Graves' ophthalmopathy

Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 2005;90:5234-40.

SUMMARY

Background Graves' ophthalmopathy is an inflammatory autoimmune disorder of extraocular muscle and fibroadipose tissue. Patients with ophthalmopathy are often treated with oral or intravenous glucocorticoids because of their potent antinflammatory and immunosuppressive activity. In this prospective study the efficacy of oral and intravenous glucocorticoid therapy was compared in patients with Graves' ophthalmopathy.

Methods The study subjects were 70 consecutive patients with moderately severe or severe active Graves' ophthalmopathy of recent onset (<6 months). Moderately severe ophthalmopathy was defined as marked soft-tissue swelling and inconstant diplopia or proptosis >25 mm, and severe ophthalmopathy as constant diplopia or optic neuropathy (swelling or pallor of the optic disk, visual-field defects, or decreased visual acuity). There were 59 women and 11 men (age range, 25 to 75 years); 41 (59 percent) were smokers. All but 2 patients had hyperthyroidism and were treated with an antithyroid drug; the other 2 had Hashimoto's thyroiditis. The patients' base-line Clinical Activity Scores (based on assessment of orbital pain at rest or eye movement; swelling of the conjunctiva, caruncle, or cornea; and conjunctival or palpebral erythema, each scored as 0 [absent] or 1 [present]) ranged from 3 to 7.

The patients were randomly assigned to receive 500 mg of methylprednisolone intravenously (IV) once weekly for 6 weeks and then 250 mg weekly for 6 weeks (total, 4.5 g); or 100 mg of prednisolone orally daily for 1 week, after which the dose was reduced by 10 mg daily at weekly intervals, and stopped after 12 weeks (total, 4 g). The patients underwent complete ophthalmic examinations (by an examiner unaware of treatment), assessment of quality-of-life using the Short Form-36 questionnaire, and ultrasonography of the orbits at base line and 12 weeks. A response to treatment was defined as 3 or more of the following changes at 12 weeks: a ≥2 mm decrease in proptosis, a ≥2 mm decrease in lid width, a ≥3 mm decrease in ocular pressure, a ≥3 mm decrease in the sum of the width of the rectus muscles, and disappearance of diplopia in primary gaze or decrease in diplopia and increase in visual acuity.

Results The base-line demographic characteristics and ophthalmologic findings in the 35 patients in each group were similar, and all patients completed the study. Among the patients who received (IV) methylprednisolone, 27 (77 percent) responded to treatment, as compared with 18 (51 percent) who received oral prednisolone (P<0.01). Ophthalmopathy worsened in 2 patients (6 percent) in the IV methylprednisolone group and 5 (14 percent) in the oral prednisolone group. The changes in some ophthalmologic findings are shown in the Table.

Table. Changes in Ophthalmologic Findings (Median Values or No. of Patients) in the Two Therapy Groups.

	IV Methylprednisolone		Oral Prednisolone	
	Base Line	12 Weeks	Base Line	12 Weeks
Lid width (mm)	13	11	12	11
Proptosis (mm)	24	22	23	22
Muscle width (mm)	27	23	26	24
Diplopia (n)	26	20	24	22
Optic neuropathy (n)	5	0	3	2

Among the patients in the IV methylprednisolone group, 21 (60 percent) had a ≥2 mm decrease in proptosis, 22 (63 percent) had a ≥2 mm decrease in lid width, and 27 (77 percent) had a 3-point decrease in Clinical Activity Score; the respective numbers in the oral prednisolone group were 14 (40 percent), 14 (40 percent), and 18 (51 percent). Quality of life improved in more patients in the former group. Smokers in either group were more likely to have worsening of ophthalmopathy during treatment.

During the 6-month period after treatment, optic neuropathy developed in 4 patients in the prednisolone group, and more patients in this group underwent orbital decompression or other ophthalmic operations.

Conclusion A 3-month course of IV methylprednisolone is more effective than oral prednisolone in ameliorating ophthalmologic symptoms and improving vision in patients with Graves' ophthalmopathy.

COMMENTARY

The patients in this study were carefully selected and followed, and the results seem clear—intravenous methylprednisolone was more effective than oral prednisolone. There seem to have been few exacerbations of ophthalmopathy after treatment was stopped in either group, but this has been a problem in other studies. There were fewer manifestations of Cushing's syndrome (weight gain, insomnia, depression) in the methylprednisolone group.

Pulse intravenous glucocorticoid therapy is probably the most appropriate of what may be called the aggressive therapies for Graves' ophthalmopathy, the others being retroorbital radiation and orbital decompression. What is less clear are the indications for this therapy. Ideally, it would be given before ophthalmopathy becomes as severe as in the patients studied by Kahaly et al. But progression to that level of severity is uncommon, and there is no way to predict it. A way to do that is needed as much as is better therapy.

Robert D. Utiger, M.D.

The risk of hypothyroidism is high in older women treated with lithium

Kirov G, Tredget J, John R, Owen MJ, Lazarus JH. A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients. J Affect Dis 2005;87:313-7.

SUMMARY

Background Lithium carbonate therapy in patients with psychiatric disorders is often associated with thyroid dysfunction, especially hypothyroidism. In this study, the frequency of thyroid dysfunction was determined cross-sectionally in a large group of patients treated with lithium and prospectively in a subset of the group.

Methods The cross-sectional study group consisted of 274 patients (159 women, 115 men) being treated with lithium for bipolar or unipolar disorder. The mean duration of lithium therapy was 73 months in the women and 80 months in the men. The prospective study group consisted of 57 of these patients (33 women, 24 men). They had normal thyroid function when first studied, had not received thyroid hormone to potentiate antidepressant drug therapy, and were followed prospectively for at least one year.

Serum thyrotropin (TSH), free thyroxine (T_4), and antithyroid peroxidase (TPO) antibodies were measured in all patients. Hypothyroidism was defined as a single serum TSH value >20 mU/L or two or more values >12 mU/L and normal or low serum free T_4 values (information provided by authors). Hyperthyroidism was defined as a low serum TSH and high free T_4 value.

Results Twenty-seven of the 159 women (17 percent) and 4 of the 115 men (3 percent) in the cross-sectional study had onset of hypothyroidism during lithium therapy (Table). The frequency of hypothyroidism was very low before approximately 45 years of age in both women and men, and it increased progressively to approximately 50 percent in women 65 years of age, but only slightly in men. Among the patients with thyroid dysfunction, 58 percent had high serum anti-TPO antibody concentrations (usually measured after the diagnosis of thyroid dysfunction).

Table. Thyroid Dysfunction among Lithium-Treated Patients.

	Women (n=159)	Men (n=115)
Hypothyroidism		
During lithium therapy	27 (17%)	4 (3%)
Before lithium therapy	5 (3%)	3 (3%)
Hyperthyroidism		
During lithium therapy	6 (4%)	2 (2%)
Before lithium therapy	2 (1%)	1 (1%)

Among the patients followed prospectively (mean follow-up, 53 months; range, 14 to 87), 4 of the 33 women (12 percent) had the onset of hypothyroidism and 1 (3 percent) hyperthyroidism caused by Graves' disease; all 5 had high serum anti-TPO antibody concentrations. The incidence rate of hypothyroidism among the women was 27 per 1000 person years of follow-up. There were no cases among the 24 men.

Conclusion Hypothyroidism occurs with increasing frequency with age in women with psychiatric disorders who are treated with lithium.

COMMENTARY

Lithium has diverse effects on thyroid function. Its basic action is to inhibit resorption of thyroglobulin (Tg) from the lumen of thyroid follicles into the cells and its subsequent proteolysis, thereby decreasing thyroid hormone secretion. It is, therefore, an antithyroid drug. When lithium therapy is initiated in patients with normal thyroid function, serum thyroid hormone concentrations fall slightly and serum TSH concentrations rise slightly, but in most patients the changes are transient. Some patients, however, have sustained subclinical or overt hypothyroidism, which may occur either soon or long after initiation of lithium therapy, as in this study. The incidence of hypothyroidism in the women in this study (27 per 1000 person-years of follow-up) was about eight times that among women in general in the same country (1).

There are strong links between chronic autoimmune thyroiditis and lithium-related hypothyroidism. The presence of high serum antithyroid antibody concentrations when lithium is begun is a risk factor for lithium-related hypothyroidism, and the concentrations are high in most patients at the time of diagnosis of hypothyroidism. The latter finding suggests that lithium therapy may itself be a risk factor for autoimmune thyroiditis. Patients with autoimmune thyroiditis are less likely to be able to maintain normal thyroid function when taking lithium than patients with no thyroid disease, just as they are less able to maintain normal thyroid function when given iodine; they cannot escape from the antithyroid action of not only iodine but also lithium.

Lithium is also a prothyroid drug, or more precisely, it is associated with hyperthyroidism, probably because of its ability to activate other autoimmune thyroid disorders. Specifically, lithium has been associated with hyperthyroidism caused by both silent or painless (subacute lymphocytic) thyroiditis and Graves' disease (2,3).

Robert D. Utiger, M.D.

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Remission of subclinical hypothyroidism can occur months or years after diagnosis

Diez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 2005;90:4124-7.

SUMMARY

Background Subclinical hypothyroidism, defined as a high serum thyrotropin (TSH) and a normal serum free thyroxine (T_4) concentration, is common. With time, it may persist, disappear, or progress to overt hypothyroidism. The time course of disappearance of subclinical hypothyroidism, defined as normalization of serum TSH concentrations, was determined in this study.

Methods The study subjects were 40 patients with subclinical hypothyroidism whose serum TSH concentrations decreased to within the normal range during follow-up. They were part of a group of 107 patients aged 55 years or older who had subclinical hypothyroidism that had persisted for 1 to 3 months, after which they were enrolled in the study and evaluated at 6-month intervals for up to 72 months. Among the other 67 patients, overt hypothyroidism developed in 28, and 39 had persistent subclinical hypothyroidism. None had a history of any thyroid disease.

Results There were 32 women and 8 men (mean age, 63 years). At base line, 3 patients had a goiter, 15 had some symptoms of hypothyroidism, and 24 had a high serum concentration of antithyroid peroxidase (TPO) antibodies. Five patients had diabetes mellitus, 11 had hypertension, and 13 had hyperlipidemia. Their mean (±SD) serum TSH concentration (normal, 0.4 to 5.0) was 7.5±1.8 mU/L; the concentration was ≥10 mU/L in only 3 of the 40 patients. Their mean serum free T_4 concentration was 1.08±0.19 ng/dl (13.9±2.4 pmol/L) (normal, 0.8 to 2.0 [9.7 to 25.7]).

The patients' serum TSH concentrations decreased to within the normal range in 6 to 60 months (median, 18 months). The decrease occurred during the first year of follow-up in 15 patients (38 percent), the second year in 12 (30 percent), the third year in 3 (7 percent), and the fourth or fifth year in 10 (25 percent). At that time, their mean serum TSH concentration was 3.4±1.1 mU/L and their mean serum free T_4 concentration was 1.14±0.18 ng/dl (14.7±2.3 pmol/L). The mean decrease in serum TSH concentration was 4.1±2.0 mU/L. There was no correlation between age, sex, or serum anti-TPO antibody concentration at base line and the fall in serum TSH concentration or the final serum TSH concentration.

Conclusion Among older patients with subclinical hypothyroidism, serum TSH concentrations may become normal as long as five years after diagnosis. Most have base-line serum TSH concentrations of >5 to 10 mU/L, and remission is not related to age, sex, or serum anti-TPO antibody concentration at that time.

COMMENTARY

A strength of this study was that the patients had high serum TSH values on two occasions 1 to 3 months apart before enrollment (1). Therefore, they were more likely to have some thyroid disorder than those with a single high value. Nevertheless, 40 of the 107 patients (37 percent) did have normal values later, of whom 37 had a base-line serum TSH concentration <10 mU/L (altogether, 71 patients had a base-line serum TSH concentration <10 mU/L).

Why does mild subclinical hypothyroidism remit? In considering this question, it is important to remember that a decrease in thyroid secretion of only 10 to 20 percent for a few weeks will result in an increase in serum TSH concentrations to 5 to 10 mU/L, and this increase will often restore thyroid and then TSH secretion to normal. For high serum TSH concentrations (e.g., subclinical hypothyroidism) to persist, the ability of the thyroid to respond to TSH has to be impaired, so that continued TSH hypersecretion is needed to maintain near-normal thyroid secretion. When whatever is decreasing thyroid secretion and limiting the thyroidal response to TSH subsides, be it chronic autoimmune thyroiditis, some other thyroid disorder, or some unrecognized dietary or environmental antithyroid agent, thyroid and then TSH secretion will return to normal.

Will the remission that occurred in these patients be durable? Not necessarily. The patients apparently had only one serum TSH value within the normal range, and there was no further follow-up. At that time the value in some patients was only 2 to 3 mU/L lower than at base line, and the mean value was 3.4 mU/L, not far from the upper limit of the normal range.

Nonetheless, the fact that 37 of 71 patients (52 percent) with base-line serum TSH concentrations <10 mU/L on two occasions later had normal serum TSH concentrations (and higher serum free T_4 concentrations) argues against routine treatment of all patients with subclinical hypothyroidism. Can patients likely to have a remission be identified prospectively? The base-line characteristics of the patients who had a remission and those who had persistent subclinical hypothyroidism are not described, but it seems unlikely that they differed much.

Robert D. Utiger, M.D.

Reference

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Initiation of therapy with a full dose of thyroxine in patients with hypothyroidism is safe and convenient

Roos A, Linn-Rasker SP, van Domburg RT, Tijssen JP, Berghout A. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. Arch Intern Med 2005;165:1714-20.

SUMMARY

Background The standard treatment for hypothyroidism is thyroxine (T_4), usually given initially in full replacement doses to young patients, but in lower doses to older patients. In this study, the effects of initiation of therapy with a replacement dose of T_4 and a low dose of T_4 were compared in patients with hypothyroidism.

Methods The study subjects were 50 patients (39 women, 11 men; mean age, 47 years [range, 22 to 86]) with overt hypothyroidism (serum thyrotropin [TSH], >4.2 mU/L; free thyroxine [T_4], <0.78 ng/dl [10 pmol/L]) caused by chronic autoimmune thyroiditis. Patients with a history of cardiac disease or hypertension were excluded. The results of echocardiography and dobutamine stress echocardiography were normal in all patients at base line.

The patients were randomly assigned to receive T_4 in a dose of 1.6 µg/kg/day (full-dose group) or 25 µg/day (low-dose group). In both groups the doses were adjusted in 25–µg increments every 4 weeks for 24 weeks and then every 12 weeks for 48 weeks, with the goal of normal serum TSH and free T_4 concentrations. The T_4 was given in 1 ml of liquid at bedtime. At base line and the times described above, the patients completed a 12-item hypothyroid symptom score; serum TSH, free T_4, lipids, and homocysteine were measured; and electrocardiography was performed. Other tests done less often included another 10-item hypothyroid symptom questionnaire, a 36-item general health questionnaire, and bicycle ergometry.

Results The base-line characteristics of the patients in each group were similar. In the full-dose group, the mean daily dose of T_4 increased from 128 µg (1.6 µg/kg) to 139 µg (1.7 µg/kg). In the low-dose group, the dose was increased regularly until 16 weeks, at which time it was 110 µg (1.5 µg/kg) daily, and it did not change thereafter. At base line, the median serum TSH concentrations were 61 and 48 mU/L, respectively, in the full-dose and low-dose groups, and the respective values at 4 weeks were 4.2 and 26.7 mU/L. The values in the full-dose group declined slightly in the next 4 weeks, but changed little thereafter, whereas the values in the low-dose group continued to decline slowly, and were not normal until 16 weeks. The mean serum free T_4 concentration increased substantially at 4 weeks, but changed little thereafter, in the full-dose group, whereas it increased gradually in the low-dose group, reaching the same level as in the full-dose group at 16 weeks. Most of the patients in the full-dose group, but only a few patients in the low-dose group, had normal serum TSH and free T_4 concentrations at 8 weeks (Table).

Table. Number (Percent) of Hypothyroid Patients with Normal Serum TSH and Free T_4 Concentrations at Different Intervals According to Starting Dose of T_4.

	4 Weeks	8 Weeks	16 Weeks	24 Weeks
Full-dose group (n=25)	13 (52%)	19 (76%)	20 (80%)	21 (84%)
Low-dose group (n=25)	1 (4%)	3 (12%)	14 (56%)	20 (80%)

No patient had palpitations, tachycardia, or cardiac symptoms at any time, including during bicycle ergometry. The scores on the three questionnaires improved at the same rate and reached the same final values (at 24 weeks) in both groups. Body weight, heart rate, and blood pressure did not change in either group. The mean serum low-density lipoprotein cholesterol and homocysteine concentrations decreased slightly, and in parallel, in both groups. Exercise performance increased slightly in the high-dose group.

Conclusion In patients with hypothyroidism, initiating therapy with a full dose of T_4 is convenient and safe, but not more rapidly effective in relieving symptoms than a lower dose.

COMMENTARY

Numerous textbooks and guidelines recommend that older patients with hypothyroidism, especially those with cardiovascular disease, be treated with T_4 very conservatively, because of the risk of inducing angina, myocardial infarction, arrhythmia, or heart failure. The basis for this recommendation is largely anecdotal, although patients who had angina that worsened or who had the onset of angina when given thyroid hormone have been described (1).

Why risk an adverse effect, even if the risk is very low? What is important is that the patient's hypothyroidism was recognized. Whether serum T_4 and TSH concentrations are restored to normal sooner or later seems unimportant, especially since the rates of symptomatic improvement in the two groups in this study were similar. On the other hand, an overly conservative approach does result in some inconvenience and more testing. A reasonable compromise might well be to start with 50 percent of the estimated full replacement dose in older patients.

Robert D. Utiger, M.D.

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The antitumor drug imatinib increases the requirement for thyroxine in patients with hypothyroidism

De Groot JW, Zonnenberg BA, Plukker JT, van Der Graaf WT, Links TP. Imatinib induces hypothyroidism in patients receiving levothyroxine. Clin Pharmacol Ther 2005:78:4334-8.

SUMMARY

Background Imatinib mesylate (Gleevec®) selectively inhibits the constitutive tyrosine kinase activity of the BCR-ABL fusion protein in chronic myeloid leukemia cells and that of mutated platelet-derived growth factor receptors and c-kit receptors in gastrointestinal stromal-cell tumors. It is now widely used in patients with these tumors, and is also being given experimentally to patients with medullary thyroid carcinoma because it may inhibit the tyrosine kinase activity of the mutated RET protooncogene found in these tumors. This paper describes eight patients with hypothyroidism who needed higher doses of thyroxine (T_4) when treated with imatinib.

Methods Thyroid function was assessed repeatedly in 11 patients (4 women, 7 men; mean age, 52 years) during treatment with imatinib. Ten of the patients had medullary thyroid carcinoma and one a gastrointestinal stromal-cell tumor. Seven of the patients with medullary carcinoma and the patient with the stromal-cell tumor had postoperative hypothyroidism (the latter after surgery for follicular carcinoma of the thyroid) and were taking T_4 when given imatinib. The other three patients with medullary carcinoma had normal thyroid function.

Serum thyrotropin (TSH), free T_4, and free triiodothyronine (T_3) were measured before imatinib was started and at 2- to 4-week intervals during imatinib therapy in most patients. In the patients with hypothyroidism the dose of T_4 was raised to maintain normal serum TSH values.

Results Before imatinib therapy, the eight patients with hypothyroidism had low or normal serum TSH concentrations and normal serum free T_4 concentrations while taking 100 to 225 µg of T_4 daily (Table). During imatinib therapy (400 to 800 mg daily), all eight patients had symptoms of hypothyroidism, high serum TSH concentrations, and lower serum free T_4 concentrations. The changes in serum free T_3 concentrations paralleled those of serum free T_4, but were smaller in magnitude.

Table. Mean (Range) Dose of T_4 and Serum TSH and Free T_4 Concentrations before and during Imatinib Therapy in Eight Patients with Postoperative Hypothyroidism.

	Before Imatinib Therapy	During Imatinib Therapy
Dose of T_4 (µgday)	153 (100-225)	255 (150-400)
Serum TSH (mU/L)	0.8 (0.02-1.7)	32.2 (9.6-15.8)*
Serum free T_4 (ng/dl)	1.5 (1.2-1.8)	1.0 (0.8-1.1)*

*Overall mean values, calculated from the means of multiple measurements in each patient. To convert free T_4 values to pmol/L, multiply by 12.9.

Hypothyroidism occurred within 2 weeks after imatinib was started in some patients. The mean increase in dose of T_4 was 14 percent after 6 to 8 weeks, 33 percent after 12 to 16 weeks, and 47 percent after 26 to 32 weeks. Despite higher T_4 doses, serum TSH concentrations fell to normal in only three of these eight patients before imatinib was stopped, but they did fall to normal in all five patients who stopped imatinib. In one patient who had a high serum TSH value while taking imatinib, taking the daily doses of T_4 and imatinib 5 hours apart for a month did not result in a fall in serum TSH. Serum thyroxine-binding globulin, measured in two patients, increased slightly (14 and 23 percent).

The three patients who had normal thyroid function had no changes in serum TSH or free T_4 concentrations while taking imatinib.

Conclusion Imatinib is an anticancer drug that increases the need for T_4 in patients with hypothyroidism. The mechanism of this effect is uncertain, but it is probably caused by an increase in T_4 clearance.

COMMENTARY

The list of drugs that decrease the efficacy of exogenous T_4 and therefore increase the need for T_4 in patients with hypothyroidism grows. Possible mechanisms include inhibition of absorption of T_4, an increase in production of thyroxine-binding globulin, inhibition of T_4 transport into cells, and an increase in T_4 clearance. The latter might occur as a result of an increase in the activity of one or more cytochrome (CYP) P450 isoenzymes or an increase in hepatic glucuronyl transferase activity. The available evidence, though sparse, suggests that imatinib does not block T_4 absorption or raise serum thyroxine-binding globulin concentrations enough to raise serum TSH concentrations as much as in these patients. No drug that inhibits T_4 transporters in vivo has yet been described, and, at least two-dimensionally, imatinib doesn't look much like T_4. Imatinib inhibits, not stimulates, CYP 3A4 and CYP2D6 activity (1). This leaves increased glucuronyl transferase activity as the likely explanation, which puts imatinib in the same class as phenytoin, carbamazepine, and rifampin with respect to exacerbating hypothyroidism in patients taking T_4.

The authors do not say whether imatinib had any beneficial effects in the patients with medullary carcinoma, but it was stopped in five patients because of side effects or tumor progression.

Robert D. Utiger, M.D.

Reference

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Late hypothyroidism is common in women with postpartum thyroiditis

Azizi F. The occurrence of permanent thyroid failure in patients with subclinical postpartum thyroiditis. Eur J Endocrinol 2005;153:367-71.

SUMMARY

Background Postpartum thyroiditis is subacute lymphocytic thyroiditis that by arbitrary definition occurs within a year after parturition or miscarriage. It is characterized by hyperthyroidism, hypothyroidism, or hyperthyroidism followed by hypothyroidism. The thyroid dysfunction may be subclinical or overt, and is usually transient, but some of these women later have hypothyroidism or goiter, e.g., chronic autoimmune thyroiditis. This study was done to determine the long-term outcome of postpartum women with subclinical or overt hypothyroidism who were treated with thyroxine (T_4) and in whom the T_4 later was stopped.

Methods The study subjects were 172 women who presented with subclinical or overt hypothyroidism 3 to 10 months postpartum (mean, 6) and who had been treated with T_4. A minority had transient hyperthyroidism 2 to 4 months postpartum. All had some symptoms of hypothyroidism or had noted thyroid enlargement, all had palpable thyroid enlargement, 160 (93 percent) had diffuse or multifocal hypoechogenicity on ultrasonography, 137 (80 percent) had a high serum anti-thyroid peroxidase (TPO) antibody concentration, and 116 (67 percent) had a high serum antithyroglobulin antibody concentration (both values were high in 94 [55 percent]). Thyroid radioiodine uptake, measured in 50 women who were not nursing, was <7 percent at 24 hours in all. There were 27 women (16 percent) with subclinical hypothyroidism (mean age, 29 years; estimated thyroid weight, 32 g; serum TSH, 28 mU/L [normal, ≤5.0]; serum free T_4 index, 4.9 [normal, ≥4.5]), and 145 (84 percent) with overt hyperthyroidism (mean age, 29 years; estimated thyroid weight, 31 g; serum TSH, 64 mU/L; serum free T_4 index, 2.2).

The women were treated with T_4 because of goiter or symptoms of hypothyroidism. They were seen at 3- to 6-month intervals, at which times the dose of T_4 was changed if their serum TSH concentrations were <0.3 or >3.0 mU/L. Therapy was stopped after 12 to 84 months; the mean duration of therapy was 24 months in the women with subclinical hypothyroidism and 23 months in those with overt hypothyroidism. Thereafter, the women were seen monthly for 6 months, at 9, 12, 18, 24, 36, and 48 months, and then yearly. Serum TSH and free T_4 index were measured at each visit.

Results The median duration of follow-up after T_4 was stopped until the onset of hypothyroidism or last evaluation was 16 months (range, 1 to 120). The frequency of subclinical or overt hypothyroidism, its time of onset after cessation of T_4, and the biochemical findings (except for serum TSH) at that time or at the last follow-up visit in the women who remained euthyroid were similar in the 27 women who originally had subclinical hypothyroidism and the 145 women who originally had overt hypothyroidism (Table).

Table. Findings on Follow-up after Cessation of T_4 Therapy in Women with Postpartum Thyroiditis Who Had Subclinical or Overt Hypothyroidism before T_4 Was Given.

	Subclinical Hypothyroidism (n=27)	Overt Hypothyroidism (n=145)
Thyroid status		
Euthyroid	11 (41%)	52 (36%)
Subclinical hypothyroidism	12 (44%)	41 (28%)
Overt hypothyroidism	4 (15%)	52 (36%)
Mean duration of follow-up (mo)	11	14
Mean serum TSH (mU/L)	16.4	29.7
Mean serum free T_4 index	5.5	5.2

Some women in both original groups had onset of hypothyroidism within 1 or 2 months after stopping T_4, and the cumulative rate in both groups was still rising at last follow-up. For example, in the subclinical-hypothyroidism group, 37, 44, 52, and 59 percent of the women had hypothyroidism 6, 12, 24, and 36 months, respectively, after stopping T_4, and the percentages were only slightly higher in the overt-hypothyroidism group.

Conclusion Women with postpartum thyroiditis who have either subclinical or overt hypothyroidism and are treated with T_4 for one or more years often develop hypothyroidism again after the T_4 is stopped.

COMMENTARY

These women had unusually severe postpartum thyroid disease, in particular hypothyroidism, because all had some clinical manifestations of hypothyroidism (or goiter) as well as the biochemical abnormalities. Therefore, it is probably not surprising that the frequency of late hypothyroidism (63 percent) was higher than reported in most follow-up studies of women with postpartum thyroiditis (approximately 25 percent).

When T_4 was stopped, some women became hypothyroid again so soon that it is likely that they already had permanent hypothyroidism (and of course it could have been permanent from the start). Finally, it is not clear whether the second episode of hypothyroidism was either symptomatic or confirmed by repeated testing. Nonetheless, the underlying message is clear—women who had hypothyroidism caused by postpartum thyroiditis are at considerable risk for hypothyroidism later, and it doesn't matter whether they had subclinical or overt hypothyroidism initially.

Robert D. Utiger, M.D.

Multinodular goiter is the most common cause of thyroid enlargement in older people

Diez JJ. Goiter in adult patients aged 55 years and older: etiology and clinical features in 634 patients. J Gerontol A Biol Sci Med Sci 2005; 60:920-3.

SUMMARY

Background Nearly all thyroid diseases result in some thyroid enlargement (goiter), but data concerning the relative frequency of the different diseases are sparse. In this cross-sectional study the frequency of different causes of goiter and the symptoms associated with the goiter were determined in older subjects.

Methods The study subjects were 634 consecutive patients (544 women and 90 men), aged 55 years or older, with goiter who were seen at an endocrine clinic in Madrid, Spain, a region of iodine sufficiency, from 1994 to 2001. A history was obtained, with attention being given to symptoms of compression of structures adjacent to the thyroid; physical examination was performed; serum thyrotropin (TSH), free thyroxine (T_4), and antithyroid peroxidase antibodies were measured; and, in some patients, imaging studies were done. The cause of the goiter was determined according to the results of physical examination and these tests. The toxic goiter groups included patients with overt and subclinical hyperthyroidism, and the Hashimoto's thyroiditis group included patients with overt and subclinical hypothyroidism (information provided by the author).

Results The most common cause of goiter was nontoxic multinodular goiter, present in 325 patients (51 percent), followed by toxic multinodular goiter, present in 151 patients (24 percent) (Table).

The goiters were larger in the patients in the two multinodular-goiter groups than in any of the other groups, but there was no correlation between age or sex and goiter size.

Table. Causes of Goiter in 634 Patients Aged 55 Years and Older.

	Women (n=544)	Men (n=90)	Total
Nontoxic multinodular goiter	283 (52%)	42 (47%)	325 (51%)
Toxic multinodular goiter	132 (24%)	19 (21%)	151 (24%)
Solitary nodule	53 (10%)	9 (10%)	62 (10%)
Toxic adenoma	24 (4%)	8 (9%)	32 (5%)
Graves' disease	19 (4%)	8 (9%)	27 (4%)
Hashimoto's thyroiditis	24 (4%)	1 (1%)	25 (4%)
Simple goiter	6 (1%)	2 (2%)	8 (1%)
Thyroiditis*	3 (1%)	0 (0%)	3 (0.5%)
TSH-secreting pituitary adenoma	0 (0%)	1 (1%)	1 (0.2%)

*All three patients had overt hyperthyroidism.

The goiter had been present considerably longer in the patients with nontoxic nodular goiter (2 to 13 years) and those with toxic multinodular goiter (1 to 12 years) than in the patients with a solitary nodule (1 to 7 years) or a toxic adenoma (0.3 to 7 years).

Some symptoms or findings related to goiter size (local symptoms, retrosternal extension, tracheal deviation, or growth) were present in 159 patients (49 percent) with nontoxic multinodular goiter, 73 (48 percent) with toxic multinodular goiter, 13 (21 percent) with a solitary thyroid nodule, and 17 (53 percent) with a toxic adenoma.

Conclusion The most common causes of goiter in older people are nontoxic multinodular goiter and toxic multinodular goiter.

COMMENTARY

The causes of goiter in these patients seem to have been determined primarily on the basis of physical examination, with confirmation by serologic testing and imaging. However, whether all the patients had an imaging study is not stated explicitly. Physical examination is not a reliable indicator of the presence, much less the type, of goiter. For research purposes, but not routine clinical practice, imaging studies are essential for distinguishing reliably between a solitary nodule and a multinodular goiter and between Hashimoto's thyroiditis and multinodular goiter.

The high frequency of multinodular goiter in these patients is in keeping with the results of other surveys, and the occurrence of hyperthyroidism in approximately one third of them is in keeping with the notion that these goiters contain one or more gradually enlarging nodules of autonomously functioning thyroid tissue. Therefore, thyroid hormone production gradually increases, first causing subclinical hyperthyroidism and later overt hyperthyroidism. If this formulation is correct, subclinical hyperthyroidism should be more common than overt hyperthyroidism in patients with toxic nodular goiter, but they were not distinguished in this study. One might also expect that patients with a toxic multinodular goiter would have a larger goiter than those with a nontoxic multinodular goiter. This is in general true, but the correlation between size and function is poor, for several reasons. Many of these goiters contain cystic or fibrotic regions. Some nodules have little or no capacity to produce thyroid hormone, but can grow, because of some innate characteristic or stimulation by factors like insulin-like growth factor-1. Lastly, the functional efficiency of different nodules varies. For example, some nodules have activating mutations of the TSH receptor, and the constitutive activity of the mutated receptor can vary. If the mutated receptor is highly active, the mass of tissue needed to cause hyperthyroidism will be less than if the mutated receptor is less active.

The real mystery is what initiates the process of goitrogenesis that ultimately leads to multinodular goiter.

Robert D. Utiger, M.D.

The presence of serum thyroglobulin antibodies is not related to outcome in patients with thyroid carcinoma

Gorges R, Maniecki M, Jentzen W, Sheu SN, Mann K, Bockisch A, Janssen OE. Development and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy. Eur J Endocrinol 2005;153:49-55.

SUMMARY

Background Some patients with thyroid carcinoma have high serum concentrations of antithyroglobulin (anti-Tg) antibodies. The presence of these antibodies may predict persistent or recurrent carcinoma, and also compromises measurement of serum thyroglobulin (Tg) for detecting persistent or recurrent carcinoma. In this study serum anti-Tg antibodies were measured prospectively in patients with thyroid carcinoma.

Methods The study subjects were 112 consecutive patients (81 women, 31 men; age range, 17 to 78 years) with papillary, follicular, or insular carcinoma. Serum anti-Tg antibodies were first measured a median of 23 days after thyroidectomy, when the patients had high serum thyrotropin (TSH) concentrations and just before they were treated with iodine-131 (I-131) (27 to 162 mCi [1 to 6 GBq]). Additional doses of I-131 were given to patients with persistent I-131 uptake in the thyroid region. Serum anti-Tg antibodies (assay sensitivity, 6 U/ml; normal range, 6 to 50 U/ml), TSH, and Tg were measured at 6-month intervals while the patients were taking thyroxine, and thyroid ultrasonography and other imaging studies were done if indicated. The mean (±SD) duration of follow-up was 33±8 months.

Results Serum anti-Tg antibodies were present (7 to 1531 U/ml) initially in 32 of the 112 patients (29 percent), and the concentration was high (>50 U/ml) in 22 (20 percent), all women. Of 17 patients with metastases at this time, serum anti-Tg antibodies were detectable in 1 (6 percent), as compared with 31 of 95 patients (33 percent) with no metastases. Thyroid histopathology, reviewed only in the 23 patients who had serum anti-Tg antibody concentrations >40 U/ml, was consistent with Hashimoto's thyroiditis in 10 (43 percent).

Serum anti-Tg antibodies were measured again 5 to 14 weeks after the first dose of I-131 in 42 patients. There was no change in 32 patients (the antibodies remained undetectable in 28), a decrease in 7, and an increase in 3. Among the 7 patients in whom the concentrations increased, 6 had no recurrence and 1 later had lung metastases.

Overall, 35 of the 112 patients (31 percent) had a detectable serum anti-Tg antibody concentration at least once during the follow-up period. After 8 months, serum anti-Tg antibody concentrations gradually decreased in all 35 (with some oscillation in 2 patients). Thus, serum anti-Tg antibodies were undetectable in approximately 50 percent at 1 to 1.5 years and 67 percent at 3 to 3.5 years. The median half-life of the serum anti-Tg antibodies in these 35 patients was 10 weeks (range, 3 to 120 weeks).

At 15 to 18 months after surgery, serum anti-Tg antibodies, measured in 90 patients, were present in 16 (18 percent), 1 of 7 (14 percent) with persistent tumor, 6 of 31 (19 percent) with a thyroid remnant, and 9 of 52 (17 percent) with neither. At 3 years, 103 of the 112 patients (92 percent) were in remission, 1 had stable persistent tumor, and 8 had recurrent or progressive tumor (2 had died). There was no correlation between the initial serum anti-Tg antibody value, the presence of serum anti-Tg antibodies at 15 to 18 months, or the serum anti-Tg antibody half-life and the course of the disease.

Conclusion Serum anti-Tg antibodies are present at the time of diagnosis in a substantial minority of patients with thyroid carcinoma, and they disappear gradually thereafter. Neither their presence nor their persistence is correlated with outcome in these patients.

COMMENTARY

Serum anti-Tg antibody concentrations are high in from 10 to 40 percent of patients with differentiated thyroid carcinoma at the time of diagnosis or very soon thereafter, which is more often than in normal subjects. In this study the frequency was 29 percent. Some, but not all, patients with thyroid carcinoma who have detectable serum anti-Tg antibodies have histologic evidence of autoimmune thyroiditis in addition to the carcinoma. Why other patients who have no histopathologic evidence of autoimmune thyroiditis have serum anti-Tg antibodies is not known, but one possibility is that their tumors produce abnormal forms of Tg that are immunogenic.

The key questions raised by the presence of serum anti-Tg antibodies in patients with thyroid carcinoma are whether the antibodies interfere with measurements of serum Tg, the best test for detecting persistent thyroid carcinoma, and whether persistent production of the antibodies is associated with persistent carcinoma. Both questions were addressed in this study. Serum Tg values, measured by immunoradiometric assay, were underestimated in serum samples containing anti-Tg antibodies.

The persistent production of anti-Tg antibodies was not a determinant of the persistence or recurrence of carcinoma in this study, but was in other studies. Whichever is true, when serum Tg cannot be measured with confidence, there is more concern that the patient has persistent tumor, and more complicated follow up studies are needed.

Robert D. Utiger, M.D.

Radioactive iodine and external radiation therapy are beneficial in selected patients with differentiated thyroid carcinoma

Brierley J, Tsang R, Panzarella T, Bana N. Prognostic factors and the effect of treatment with radioactive iodine and external beam radiation on patients with differentiated thyroid cancer seen at a single institution over 40 years. Clin Endocrinol (Oxf) 2005;63:418-27.

SUMMARY

Background There are substantial variations in the way that patients with papillary or follicular thyroid carcinoma are treated, particularly with respect to extent of surgery, radioactive iodine (I-131) therapy, and external-beam radiation therapy directed to the neck. This retrospective study was done to determine the effect of variations in treatment on outcome in patients with thyroid carcinoma seen at a single hospital over a period of 40 years.

Methods From 1958 to 1998, 729 patients with a new diagnosis of papillary or follicular carcinoma were seen at the Princess Margaret Hospital in Toronto. There was no consistent policy with respect to extent of surgery or treatment with I-131 or radiation. In general, patients who did not have gross residual disease after surgery were treated with a low dose of I-131. Those with gross residual disease were usually treated with higher doses and then radiation, usually in a dose of 45 to 50 Gy given in 20 fractions.

Results There were 539 women (74 percent) and 190 men (26 percent) (mean age, 47 years); 556 (76 percent) had papillary carcinoma and 173 (24 percent) had follicular carcinoma. The tumor was <1 cm in 66 patients (9 percent), 1 to 4 cm in 444 (61 percent), >4 cm in 215 (29 percent), and size not known in 4 (1 percent). There was extrathyroidal extension in 369 patients (50 percent), neck metastases in 283 (39 percent), and gross residual disease after surgery in 65 (9 percent). I-131 was given to 528 patients (72 percent) and radiation therapy to 318 (44 percent).

The median follow-up was 11 years (range, 0.3 to 40 years). The overall 10-year cause-specific survival rate was 87 percent (papillary carcinoma, 93 percent; follicular carcinoma, 70 percent) and the 10-year local-regional relapse-free rate was 85 percent (papillary carcinoma, 85 percent; follicular carcinoma, 83 percent). Age <45 years, female sex, papillary histology, smaller tumor size, absence of gross residual disease, and absence of metastasis on first post-I-131 therapy scan were associated with higher 10-year cause-specific survival rates. Among these factors, age <45 years, smaller tumor size, and absence of gross residual disease were associated with higher 10-year local-regional relapse-free rates. The presence of neck metastases did not affect survival, but was associated with a higher local-regional relapse rate.

Overall, more aggressive surgery or I-131 therapy was not associated a higher cause-specific survival rate, but I-131 therapy was associated with a lower local-regional relapse rate (hazard ratio, 0.5; P=0.007). Among 324 patients <45 years old with tumors <1 cm and no gross residual disease or metastases, 228 (70 percent) were treated with I-131. The 10-year cause-specific survival rate was lower in the patients who were treated with I-131 (97 vs. 100 percent; P=0.04), but the 10-year local-regional relapse-free rates were similar (90 vs. 85 percent; P=0.32).

There were 154 patients with papillary carcinoma and microscopic residual disease (tumor at or within 2 mm of the resection margin), but no gross residual disease or metastases, of whom 90 were treated with radiation and 64 were not. The respective 10-year cause-specific survival rates were 100 and 95 percent (P=0.01), and the respective 10-year local-regional relapse-free rates were 94 and 84 percent (P=0.02). In patients ≥45 years old with extrathyroidal extension but no gross residual disease, there was no benefit of radiation. In patients >60 years old with extrathyroidal extension but no gross residual disease, radiation therapy was beneficial; the 10-year cause-specific survival rate was higher in the treated patients, than in those who were not treated (81 vs. 65 percent; P=0.04), as was the 10-year local-regional relapse-free rate (86 vs. 66 percent; P=0.01).

Conclusion Among patients with papillary or follicular carcinoma, factors associated with a good prognosis are younger age, female sex, and limited extent of disease. I-131 therapy and radiation therapy have benefit in some patients.

COMMENTARY

The results of this study make clear both the value and hazard of subgroup analyses. Looked at globally, more extensive surgery or I-131 therapy had little benefit, but I-131 and also radiation therapy did have benefit in selected subgroups. One problem is determining to which subgroup a patient belongs. It is easy to determine the size of a tumor, but categorization of extrathyroidal extension (seen by the surgeon or pathologist), gross residual disease (seen by the surgeon at the end of the operation), and neck metastasis (seen by the surgeon or pathologist) is harder, and in individual patients the categorizations may be contradictory.

One of the features of this study was the high percentage (44 percent) of patients who were treated with external-beam radiation. It was of benefit in patients with microscopic residual disease and in patients >60 years old with extrathyroidal extension but no gross residual disease but not in similar patients aged ≥45 to 60 years. At most places, the patients most likely to be treated with radiation are those with gross residual disease. There were 65 patients in that group in this study, but how many were treated with radiation and their outcome are not described.

Robert D. Utiger, M.D.

An increase in serum thyroglobulin after thyrotropin administration indicates persistent tumor in patients with thyroid carcinoma

Kloos RT, Mazzaferri EL. A single recombinant humanthyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 2005;90:5047-57.

SUMMARY

Background Measurements of serum thyroglobulin (Tg), both basally and in response to endogenous or exogenous thyrotropin (TSH) stimulation, have become indispensable for the follow-up of patients with differentiated thyroid carcinoma. This study determined the course of patients with thyroid carcinoma in whom serum Tg had been measured after exogenous TSH stimulation several years earlier.

Methods The study subjects were 107 patients (88 women, 19 men) with differentiated thyroid carcinoma (papillary carcinoma, 89; follicular or Hurthle-cell carcinoma, 18). They were 11 to 85 years old [median, 36]) at the time of initial treatment (total or near-total thyroidectomy, with varying degrees of lymph-node resection, and radioactive iodine [I-131]).

Between 1999 and 2001, 1 to 35 years (mean, 7) after initial treatment, serum Tg was measured both basally during thyroxine (T_4) therapy and 72 hours after the second of two 0.9-mg intramuscular doses of recombinant human TSH (rhTSH) given on two consecutive days. Basal serum Tg values were <0.5 ng/ml in 102 patients (95 percent), 0.6 ng/ml in 4 patients (4 percent), and 1.0 ng/ml in 1 patient (1 percent). After rhTSH stimulation, serum Tg values were ≤0.5 ng/ml in 68 patients (63 percent), 0.6 to 2.0 ng/ml in 19 patients (18 percent), and >2.0 ng/ml in 20 patients (19 percent). No patient who had a rhTSH-stimulated serum Tg value ≤2.0 ng/ml had any evidence of persistent tumor. Among the 20 patients who had rhTSH-stimulated serum Tg values >2.0 ng/ml, persistent tumor was identified (and treated) in 9 and suspected on the basis of high serum Tg values alone in 2. The basal serum Tg values in these 11 patients were ≤5 ng/ml in 7 and 0.6 to 1.0 ng/ml in 4.

These patients were followed from 2001 to 2004. They were considered free of disease at the end of follow-up if ultrasonography of the neck was negative and their basal serum Tg values were <0.5 ng/ml on two or more occasions or their stimulated serum Tg values (after either rhTSH stimulation or withdrawal of T_4 and endogenous TSH stimulation) were <0.5 ng/ml on one or more occasions.

Results Follow-up data were available for 101 of the original 107 patients (94 percent); none of those lost to follow-up had evidence of disease when last seen. The mean duration of follow-up from the first rhTSH stimulation test was 3 years (range, 1 to 5), and the mean duration of follow-up from initial treatment was 9 years (range, 2 to 39). At study end, 95 patients (94 percent) had basal serum Tg values <0.5 ng/ml, and the values ranged from 0.9 to 6.2 ng/ml in 6 (6 percent).

Among 63 patients whose first rhTSH-stimulated serum Tg values were <0.5 ng/ml, all had basal and stimulated serum Tg values <0.5 ng/ml during follow-up. One patient later had a high serum concentration of anti-Tg antibodies and then was found to have persistent tumor in cervical lymph nodes. Among the 18 patients whose first rhTSH-stimulated serum Tg values were 0.6 to 2.0 ng/ml, basal or stimulated serum Tg values during follow-up were <0.5 ng/ml in 13 and stimulated values were 0.7 to 3.4 ng/ml in 5; tumor was found only in the patient whose stimulated serum Tg value was 3.4 ng/ml. Among the 20 patients whose first rhTSH-stimulated serum Tg value was >2.0 ng/ml, 15 had basal serum Tg values <0.5 ng/ml and 14 had stimulated values >2.0 ng/ml during follow-up. Persistent tumor had been found or suspected initially in 9, and was found in 7 others during follow-up, but at last follow-up 11 (55 percent) had no evidence of tumor.

Conclusion Patients with papillary or follicular thyroid carcinoma who have a high serum rhTSH-stimulated serum Tg value (>2.0 ng/ml) after initial surgery and I-131 treatment are likely to have persistent tumor, but it may not be detectable at the time of the stimulation test.

COMMENTARY

The results of the first rhTSH-stimulated serum Tg test done in these patients, summarized above, were reported in detail prewiously (1). The emphasis in both studies was on the value of measurements of rhTSH-stimulated serum Tg for predicting the presence of persistent tumor, but the results of basal serum Tg measurements were almost as valuable. Specifically, the sensitivity, specificity, positive predictive value, and negative predictive value of a basal serum Tg value >0.5 ng/ml for predicting persistent tumor then (first study) or overall (this study) were almost as high as the respective values for rhTSH-stimulated serum Tg values >2.0 ng/ml, the major exception being the lower sensitivity of the basal serum Tg value. One TSH stimulation test after initial treatment, and it doesn't matter whether the stimulation is effected by exogenous or endogenous TSH, is sufficient for many patients, and even that may be too many for some, for example, low-risk patients with persistently undetectable serum Tg concentrations while taking T_4.

Robert D. Utiger, M.D.

Reference

1. Mazzaferri EL, Kloos RT. Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab 2002; 87:1490-8.

Autoimmune thyroid disease and thyroid dysfunction are complications of interferon-β therapy in patients with multiple sclerosis

Caraccio N, Dardano A, Manfredonia F, Manca L, Pasquali L, Iudice A, Murri L, Ferrannini E, Monzani F. Long-term follow-up of 106 multiple sclerosis patients undergoing interferon-β 1a or 1b therapy: predictive factors of thyroid disease development and duration. J Clin Endocrinol Metab 2005;90:4133-7.

SUMMARY

Background Many patients with multiple sclerosis are treated with interferon-β, an immunomodulatory molecule that is known to activate autoimmune thyroid disease. Most studies of thyroid disorders in patients treated with interferon-β have been relatively short-term, and the extent to which the risk of these disorders persists when treatment is continued is not known. In this study thyroid function and autoimmunity were assessed periodically in patients treated for as long as 84 months.

Methods The study subjects were 106 patients (76 women, 30 men; mean [±SD] age, 36±10 years) with remitting–relapsing multiple sclerosis. None had received other therapy for at least one month before interferon was started. Fifty-seven patients were treated with interferon-β 1a (natural-sequence recombinant), given weekly, and 49 were treated with interferon-β 1b (modified recombinant), given on alternate days.

Serum thyrotropin (TSH), free thyroxine (T_4), free triiodothyronine (T_3), and antithyroid peroxidase (TPO), antithyroglobulin (Tg), and TSH-receptor antibodies were measured at base line, every three months for one year, and every six months thereafter.

Results At base line, 3 patients (3 percent) had subclinical hypothyroidism. Among the 103 patients with normal thyroid function at that time, 25 (24 percent) had incident thyroid dysfunction (hypothyroidism, 20 patients; hyperthyroidism, 5 patients) during a median follow-up period of 42 months (range, 12 to 84) (Table). Hypothyroidism was permanent (not defined) in 11 of the 20 patients (55 percent), but there were no cases of permanent hyperthyroidism.

Table. Incident Thyroid Disorders in Patients with Multiple Sclerosis Treated with Interferon-β.

	Interferon-β 1a (n=57)	1aInterferon-β 1b (n=49)
Hypothyroidism		
Subclinical	11 (19%)	8 (16%)
Overt	—	1 (2%)
Transient/permanent	6/5	3/6
Hyperthyroidism		
Subclinical*	1 (2%)	3 (6%)
Overt*		1 (2%)
Transient/permanent	1/0	4/0

*All patients with hyperthyroidism had decreased thyroid uptake of pertechnetate-99m.

At base line, 9 patients (8 percent) had a high serum antithyroid antibody concentration, of whom 7 later had thyroid dysfunction. Among the 97 patients who had normal values, 22 (23 percent) had high values during follow-up. Nine patients had a high serum anti-TPO antibody value, 10 a high serum anti-Tg antibody value, 2 high values for both antibodies, and 1 a high serum TSH-receptor antibody value. Twelve of these 22 patients (54 percent) remained euthyroid, and 10 (45 percent) had thyroid dysfunction, usually with onset later. The high values were transient in 13 of the 22 patients (59 percent).

The onset of high serum antithyroid antibody values and thyroid dysfunction was within the first year of treatment in 76 and 68 percent, respectively, of those affected at any time. The results in the patients treated with interferon-β 1a and those treated with interferon-β 1b were similar.

Conclusion Both thyroid autoimmune disease and thyroid dysfunction can occur in patients with multiple sclerosis who are treated with interferon-β. The former usually precedes the latter, and both usually occur during the first year of therapy.

COMMENTARY

Thyroid autoimmunity, as manifested by high serum antithyroid antibody concentrations, and thyroid dysfunction may not be quite as common in patients treated with interferon-β as in those treated with interferon-α. When they occur, however, the changes are quite similar. Serum antithyroid antibody concentrations rise during the first months of therapy, followed by subacute (silent) lymphocytic thyroiditis, manifested by hyperthyroidism, or hypothyroidism, or hyperthyroidism followed by hypothyroidism (three patients in this study). Both the hyperthyroidism and hypothyroidism are usually subclinical and transient, and therefore the frequency of detection will be determined by how often the patients are studied. These facts also make the value of screening for thyroid autoimmunity or thyroid dysfunction in patients treated with interferon-β (or interferon-α) problematic.

Robert D. Utiger, M.D.

Statin drugs may improve thyroid function in patients with Hashimoto's thyroiditis

Gullu A, Emral R, Bastemir M, Parkes AB, Lazarus JH. In vivo and in vitro effects of statins on lymphocytes in patients with Hashimoto's thyroiditis. Eur J Endocrinol 2005;153:41-8.

SUMMARY

Background Hashimoto's thyroiditis is characterized by the intrathyroidal accumulation of activated cytotoxic T lymphocytes, which may kill thyroid follicular cells by inducing programmed cell death (apoptosis). Statins are drugs that inhibit the synthesis of cholesterol and its precursors, and may also have immunomodulatory actions, including inhibition of lymphocyte proliferation and the cytotoxic actions of lymphocytes. This study evaluated the effects of statins on thyroid function and circulating lymphocytes in patients with Hashimoto's thyroiditis and also their effects on lymphocytes in vitro.

Methods The in vivo studies were done in 21 patients (19 women, 2 men; age range, 28 to 48 years) with subclinical hypothyroidism caused by Hashimoto's thyroiditis. All the patients had high serum thyrotropin (TSH) concentrations and normal serum free thyroxine (T_4) concentrations (for six months), goiter, high serum concentrations of antithyroid peroxidase (anti-TPO) or antithyroglobulin (anti-Tg) antibodies, and lymphocytic infiltration of the thyroid, as determined by fine-needle aspiration biopsy. They were randomly assigned to receive simvastatin, 20 mg daily, or no treatment for 8 weeks. Serum TSH, free T_4, anti-TPO and anti-Tg antibodies, and C-reactive protein were measured at base line and 8 weeks. The percentages of suppressor (CD8) T cells, helper (CD4) T cells, natural killer (CD16, CD56) cells, activated T cells (CD25), and B (CD19) cells in peripheral blood were also determined at these times.

For the in vitro studies, mononuclear cells were isolated from the peripheral blood of 10 other patients with Hashimoto's thyroiditis and 10 normal subjects. The cells were incubated for 72 hours with varying concentrations of cervistatin, mevastatin, pravastatin, and simvastatin, after which the proportions of CD3, CD4, and CD8 cells undergoing apoptosis were measured by flow cytometry.

Results Clinical Studies Treatment with simvastatin resulted in a rise in serum free T_4 and a fall in serum TSH concentrations, but no significant change in serum anti-TPO or anti-Tg antibody concentrations (Table). There was an increase in CD4 cells (44 to 47 percent), a decrease in CD8 cells (32 to 25 percent), an increase in B cells (10 to 12 percent), a decrease in natural killer cells (20 to 15 percent), and a decrease in activated T cells (13 to 9 percent) ($P \leq 0.05$ for all comparisons). Serum C-reactive protein decreased from 6.5 to 3.4 mg/L ($P=0.06$). There were no changes in the 10 untreated patients.

Table. Serum TSH, Free T_4, and Anti-TPO and Anti-Tg Antibody Concentrations in 11 Patients with Hashimoto's Thyroiditis before and after Administration of Simvastatin for Eight Weeks.

	Before	After
Serum TSH (mU/L)	7.7 (6.3-14.6)	4.6 (2.8-8.9)*
Serum free T_4 (ng/dl)	1.0±0.1	1.1±0.2*
Serum anti-TPO antibodies (U/ml)	1216 (166-4594)	365 (58-4136)
Serum anti-Tg antibodies (U/ml)	102 (49-286)	56 (27-229)

Values are medians (range) or means (±SD). To convert free T_4 to pmol/L, multiply by 12.9. *$P<0.05$.

In Vitro Studies Incubation of peripheral blood lymphocytes with the four statin drugs resulted in a dose-dependent increase in the proportions of CD3, CD4, and CD8 cells undergoing apoptosis. The results were similar in the cells from the patients with Hashimoto's thyroiditis and the normal subjects.

Conclusion Statin drugs improve thyroid function in patients with subclinical hypothyroidism caused by Hashimoto's thyroiditis, possibly by stimulating apoptosis of several subtypes of lymphocytes.

COMMENTARY

This provocative study suggests that statin drugs may be effective as a treatment for Hashimoto's thyroiditis. The results provide further evidence that these drugs have antiinflammatory and immunosuppressive activity, in addition to their hypocholesterolemic activity. Remarkably, statin administration was associated with a significant improvement in thyroid function in eight weeks, indicating that reducing inflammation in the thyroid can reverse thyroid injury. The authors suggest that this improvement was due to lymphocyte apoptosis, thereby ameliorating cell-mediated thyroid-cell injury. However, the rapidity of the process suggests that the drugs also decrease the production of inflammatory and cytotoxic cytokines, thereby reducing apoptosis of thyroid cells (the major mechanism of cell death in thyroiditis), before inducing lymphocyte apoptosis. Thus, statins may ameliorate thyroiditis by decreasing apoptosis of both lymphocytes and thyroid cells.

The duration of the study was short, and the benefit may not be sustained. As an example, immunosuppressive therapy in patients with type 1 diabetes results in only temporary improvement in insulin secretion and hyperglycemia. The patients had subclinical hypothyroidism, indicative of relatively mild thyroiditis and little loss of thyroid cells. Patients with overt hypothyroidism, indicative of more advanced thyroiditis and loss of more cells, may not respond as well. Statins are relatively safe drugs, but whether they indeed ameliorate hypothyroidism or prevent its progression in patients with Hashimoto's thyroiditis in the long term remains to be determined.

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A small increase in salt iodination improves iodine nutrition in children and pregnant women

Zimmermann MB, Aeberli I, Torresani T, Burgi H. Increasing the iodine content in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study. Am J Clin Nutr 2005;82:388-92.

SUMMARY

Background Iodine is an essential nutrient, and iodine supplementation is essential for maintaining iodine sufficiency in most countries. Iodine intake can decline in countries once considered iodine sufficient as a result of changes in salt intake (the foodstuff usually supplemented with iodine), food processing and intake, and animal husbandry. One country in which iodine intake declined during the 1990s was Switzerland, which led to an increase in the iodine content of salt. The effect of the increase was presumed to be substantial, because approximately 95 percent of the household salt and 70 percent of the salt used in food processing is iodized there. This study was done to determine that effect.

Methods Iodine was measured in spot urine samples collected from clusters of children in primary school and pregnant women attending prenatal-care clinics throughout Switzerland between April and December 1999 and April and September 2004. The iodine content of salt had been increased from 15 to 20 mg/kg in 1998, and it was expected that salt with the higher concentration of iodine would be used in most households by the end of 1999.

In addition, the results of blood-spot thyrotropin (TSH) measurements in newborn infants for 1992–1998 and 1999–2004 were obtained from the records of the newborn screening program for hypothyroidism for eastern Switzerland.

Results In the schoolchildren the median urinary iodine concentration increased from 115 µg/L in 1999 to 141 µg/L in 2004 (Table). The proportion of children with values >100 µg/L (indicating iodine sufficiency) increased from 60 to 76 percent, and the proportion with values >300 µg/L indicating (iodine excess) increased from 2 to 4 percent. There were no differences between girls and boys or between different age groups.

Table. Median (Range) Urinary Iodine Excretion in Schoolchildren and Pregnant Women in 1999 and 2004.

	1999	2004
Schoolchildren (no)	610	386
Age (yr)	9.5	9.9
Female (%)	50	52
Urinary iodine (µg/L)	115 (5-413)*	141 (0-516)*
Pregnant women (no)	511	279
Age (yr)	29	29
Gestational age (wk)	28	27
Urinary iodine (µg/L)	138 (5-1881)*	249 (8-995)*

*P<0.01.

In the pregnant women, the median urinary iodine concentration increased from 138 µg/L in 1999 to 249 µg/L in 2004. The proportion with values >140 µg/L (the value that corresponds to an intake of 200 to 220 µg/day, the currently recommended intake for pregnant women) increased from 48 percent in 1999 to 77 percent in 2004, and the proportion with values >500 µg/L increased from 6 percent in 1998 to 8 percent in 2004.

Blood-spot TSH concentrations were >5 mU/L in 2.9 percent of 259,035 newborn infants in 1992–1998 and 1.7 percent of 218,665 newborn infants in 1999–2004 (P<0.01), a change also indicative of increased maternal iodine intake.

Conclusion Increasing the iodine content of salt by 25 percent substantially increases urinary iodine excretion in schoolchildren and pregnant women, and fewer newborn infants have high blood-spot TSH concentrations.

COMMENTARY

Switzerland is not the only country in which there has been a decline in iodine intake in recent years; others include Australia, Colombia, Guatemala, Thailand, and the United States. It is, however, the only one that has mandated an increase in iodination of salt, with the results reported by Zimmermann et al. With respect to the consequences of iodine deficiency, such as miscarriage, preterm delivery, mental retardation, and goiter, the consequences of this increase are not known, and indeed will be difficult to detect. There was one identified benefit—fewer newborn infants with blood-spot TSH concentrations >5 mU/L—that could translate into an increase in mental capacity in later life.

Some possible reasons why iodine intake has declined in some countries are noted in the Summary above. To this list might be added exhortations to reduce the consumption of salt and some iodine-containing foods to ameliorate hypertension and hyperlipidemia. The importance of any one of them no doubt varies considerably among different households, much less different countries. Whatever the explanations, the fact that iodine intake can decline despite what seems at one time to be adequate supplementation, whether mandatory or voluntary, means that iodine nutrition must be continuously evaluated in all countries.

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Extrathyroidal triiodothyronine production is mediated primarily by type 2 iodothyronine deiodinase

Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR. Type 2 iodothyronine deiodinase is the major source of plasma T_3 in euthyroid humans. J Clin Invest 2005;115:2524-33.

SUMMARY

Background Approximately 80 percent of the triiodothyronine (T_3) in plasma is produced by the extrathyroidal deiodination of thyroxine (T_4), which is catalyzed by two iodothyronine deiodinases. Type 1 deiodinase (D1) is found mostly in the liver and kidneys and type 2 deiodinase (D2) mostly in muscle. The extent to which each deiodinase contributes to plasma T_3 is not known. In this study D1 and D2 were transiently expressed in cultured cells and the results were used to estimate their relative contribution to plasma T_3 in humans.

Methods and Results Human embryonic kidney epithelial (HEK293) cells were transfected with plasmids expressing D1 or D2. The cells were incubated with iodine-125-labeled T_4, and the I-125 iodide released was measured in the medium and sonicated cells. The rates of deiodination by D1 and D2 increased with time for up to 24 hours. Deiodination by D1, but not D2, was inhibited by propylthiouracil.

The fractional deiodination of T_4 catalyzed by D2, but not D1, decreased with increasing concentrations of T_4. At a medium free T_4 concentration of 2 pmol/L (severe hypothyroidism), the fractional conversion catalyzed by D1 was approximately 0.1 percent and that by D2 0.2 percent. At a medium free T_4 concentration of 20 pmol/L (euthyroidism), the respective rates for D1- and D2-catalyzed deiodination were each approximately 0.1 percent, and at a medium free T_4 concentration of 200 pmol/L (severe hyperthyroidism) the respective rates were 0.1 and 0.05 percent. In sonicates of the cells expressing D1, the V_{max} was approximately 8 pmol/mg protein/minute at all three T_4 concentrations, whereas it varied inversely (in the fmol/mg protein/minute range) with increasing T_4 concentrations in sonicates of cells expressing D2. Therefore, the catalytic efficiency (ratio of T_3 production in whole cells to that in cell sonicates) was considerably higher for D2.

The D2 activity of homogenates of human sternomastoid, rectus abdominis, and vastus lateralis muscle obtained at surgery was similar (0.021 to 0.024 fmol/mg protein/minute).

Based on the catalytic efficiency of D1 and D2, estimates of liver and muscle weight, and the assumption that there is no other extrathyroidal T_3 production, the contributions of liver and muscle D1 and D2 activity, respectively, to daily extrathyroidal T_3 production in a normal adult were estimated (Table). At low and normal free T_4 concentrations, D2-catalyzed deiodination would account for most extrathyroidal T_3 production, whereas D1-catalyzed deiodination would predominate at a high free T_4 concentration.

Table. Estimated Extrathyroidal (Liver and Muscle) T_3 Production in a 70-Kg Human at Three Plasma T_4 Concentrations.

	Plasma Free T_4 (pmol/L)*	Tissue Protein (g)	Organ Production of T_3 (nmol/day)**	Percent Produced by Enzyme
D1 (Liver)	2	150	2	29
	20		15	34
	200		150	67
D2 (Muscle)	2	2,240	5	71
	20		29	66
	200		74	33

*To convert to ng/dl, divide by 12.9. **To convert to µg/day, divide by 1.54.

Conclusion Both D1 and D2 contribute to the extrathyroidal production of T_3. The relative contribution of D1 increases and that of D2 decreases with rising plasma free T_4 concentrations.

COMMENTARY

Better understanding of extrathyroidal T_3 production could potentially improve the treatment of patients with hypothyroidism who do not feel well taking T_4 or a combination of T_4 and T_3 and patients with nonthyroidal illness and low serum T_3 concentrations. Toward this end, Maia et al. have developed an in vitro whole-cell model system using human D1 and D2.

The strengths of this model system include the presence in the cultured cells of the endogenous, but as yet unidentified, thiol cofactor(s) for the deiodinase reactions, the ability to detect the small amounts of T_3 produced by the cultured cells, and the ability to express enzyme activities to match those of D1 in human liver and D2 in human muscle. The estimates of the daily production of T_3 by liver D1 and muscle D2 in normal subjects are close to the estimates determined by kinetic studies after injections of tracer amounts of radiolabeled T_4. The limitations of the study are the assumptions that T_3 production by other organs can be disregarded and that plasma T_4 has equal access to liver D1 and muscle D2 in vivo, and that its access is not influenced by differences in organ blood flow or cellular T_4 transport mechanisms.

The calculations, though complex, are plausible, leading to a conclusion opposite to the long-standing assumption that most plasma T_3 is produced by liver (and kidney) D1. Instead, D2 in muscle is now predicted to be the most important source of total daily T_3 production in normal subjects and patients with hypothyroidism or nonthyroidal illness. In hyperthyroidism, T_3 production by hepatic D1 is predicted to predominate.

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