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Many people in the United States have unrecognized thyroid dysfunction

Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T_4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-99.

SUMMARY

Background Thyroid disease, especially subclinical thyroid disease, is common among patients seeking medical care, and presumably also in the population at large. This substudy of the 1988 to 1994 National Health and Nutrition Examination Survey was done to assess thyroid function in a large number of people living in the United States.

Methods The study subjects were 17,353 noninstitutionalized people aged ≥12 years living in all 50 U.S. states. Older people, blacks, and Hispanics were oversampled. Demographic, socioeconomic, and thyroid disease-related historical information was obtained, and serum was collected for measurements of thyrotropin (TSH) (normal range, 0.4 to 4.5 mU/L), thyroxine (T_4) (normal range, 4.5 to 13.2 µg/dL [58 to 170 nmol/L]), and thyroid peroxidase and thyroglobulin antibodies. The results were extrapolated to represent the total US population.

Serum TSH values >4.5 mU/L were considered high, and serum TSH values <0.1 mU/L low. Serum T_4 values >13.2 µg/dL (170 nmol/L) were considered high, and serum T_4 values <4.5 µg/dL (58 nmol/L) low. Clinical hyperthyroidism was defined as serum TSH <0.1 mU/L and a high serum T_4 value, and subclinical hyperthyroidism as a serum TSH value <0.1 mU/L and a normal serum T_4 value. Clinical hypothyroidism was defined as a serum TSH value >4.5 mU/L and a low serum T_4 value, and subclinical hypothyroidism as a serum TSH value >4.5 mU/L and a normal serum T_4 value.

Results The estimated prevalence of hypothyroidism and hyperthyroidism in the total population in 1988 to 1994, including the people self-reporting thyroid disease, was 4.6 percent (9,597,742 people) and 1.3 percent (2,610,097 people), respectively (Table).

Table. Estimated Prevalence of Hypothyroidism and Hyperthyroidism in the United States, 1988 to 1994.

	Hypothyroidism			Hyperthyroidism		
	Total (%)	Clinical (%)	Subclinical (%)	Total (%)	Clinical (%)	Subclinical (%)
Total	4.6	0.3	4.3	1.3	0.5	0.7
Whites	5.1	0.4	4.8	1.4	0.6	0.8
Blacks	1.7	0.1	1.6	1.1	0.5	0.6
Hispanics	4.1	0.2	3.9	0.7	0.2	0.5
Other	4.2	0.2	4.0	0.7	0.4	0.2

The results in the disease-free population (excluding the 4.7 percent of people with thyroid disease or receiving therapy that affects thyroid function) were as follows:

The mean serum TSH concentration was lower in blacks than in the other three groups (1.18 mU/L, vs. 1.43 to 1.57 mU/L), and the frequency of serum TSH values >4.5 mU/L was lower than in the other groups. The mean values in women and men were very similar.

The frequency of high serum TSH values increased with age; it was approximately 2 percent in the 30- to 39-year-old group, 5 percent in the 50- to 59-year-old group, and 12 percent in the 70- to 79-year-old group. In contrast, the frequency of serum TSH values <0.4 mU/L did not increase with age. The age-related changes were less in blacks than in the other groups.

Serum antithyroid peroxidase and antithyroglobulin antibody concentrations were high in 11.3 and 10.4 percent of the people, respectively. The percentage of black people who had high values was approximately 50 percent lower than that of white or Hispanic people. The frequency of high values increased with age, and was two times higher in women than in men in all racial/ethnic groups.

Conclusion Unrecognized thyroid dysfunction is common in the United States, and its frequency varies among different racial/ethic groups.

COMMENTARY

Extracting data from the paper is not easy, because the tables are complex and the definitions of the study groups vary. Furthermore, the frequency of subclinical hyperthyroidism is underestimated, because the authors chose to define a low serum TSH concentration as a value <0.1 mU/L, rather than <0.4 mU/ml, the lower limit of the normal range, and therefore did not consider values of 0.1 to 0.4 mU/L to be abnormal. The basis for this definition is said to be that serum TSH values between 0.1 and 0.39 mU/L are "clinically insignificant". That may be true, but then why are all serum TSH values >4.5 mU/L, the upper limit of the normal range, considered abnormal (and by inference clinically significant)? There is no more reason to consider serum TSH values of 7.0 or 8.0 mU/L to be clinically important than values of 0.2 or 0.3 mU/L.

Accepting that many people in the United States have unrecognized thyroid dysfunction (keep in mind that thyroid function was assessed only once), would recognition and treatment have benefits that outweighed the risks of misdiagnosis and inappropriate therapy?

Robert D. Utiger, M.D.

Serum thyrotropin and thyroid hormone concentrations vary from month to month in normal subjects

Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T_4 and T_3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 2002;87:1068-72.

SUMMARY

Background The reference ranges for serum thyrotropin (TSH), thyroxine (T_4), and triiodothyronine (T_3) concentrations in normal subjects are broad, which helps to explain the high frequency of subclinical thyroid disease (high or low serum TSH concentrations and normal serum T_4 and T_3 concentrations). The variations are due to analytical and biologic variation, which may include circadian and seasonal variation both within and between subjects. This study was done to determine the extent of variation within and between normal subjects over a one-year period.

Methods The study subjects were 16 normal men living in Denmark. Their median age was 38 years (range, 24 to 52), mean body-mass index was 25.4 kg/m^2 body-surface area (range, 21.3 to 30.9), and the median urinary iodine excretion was 50 µg/L. None had a goiter or was taking any medication. The men's diet and activities were not restricted. Blood samples for measurement of serum TSH, T_4, T_3, and T_3-resin uptake (for calculation of the free T_4 index) were collected between 0900 and 1200 hours monthly for 12 months. The samples were analyzed at the end of the study. The analytical coefficients of variation of the assays varied from 2.2 to 4.0 percent. The results from one man who had persistently low serum TSH concentrations and high serum T_3 concentrations on several occasions were excluded from the calculations.

Results There were substantial variations within subjects and even larger variations between subjects for all measurements, so that thyroid function in each man was unique (table). The 2 SD range for each man was approximately half that for the group as a whole, indicating that an individual man could have a large change in serum TSH, T_4, or T_3 concentrations or serum free T_4 index values, yet the values remain within the group or reference range.

Table. Variation in Serum TSH, T_4, and T_3 Concentrations in 15 Normal Men over a One-Year Period.

	Serum TSH (mU/L)	Serum T_4 (µg/dL)*	Serum Free T_4 Index	Serum T_3 (ng/dL)*
Range of individual mean (±2 SD) values	0.48 (0.32-0.64) to 2.42 (1.60-3.24)	6.3 (4.9-7.7) to 10.6 (10.1-11.2)	6.5 (5.0-7.9) to 10.5 (9.4-11.5)	69 (29-107) to 140 (124-157)
Group mean (±2 SD) values	1.27 (0.16-2.39)	8.2 (5.0-11.5)	7.9 (4.7-11.2)	109 (65-154)
Reference range	0.3-5.0	4.6-10.8	5.4-10.8	80-180

*To convert serum T_4 and T_3 values to nmol/L, multiply by 12.9 and 0.015, respectively.

There was a weak positive correlation between serum TSH concentrations and serum T_4 and T_3 concentrations and serum free T_4 index values. Based on the analytical and within-subject variations, highly precise (90 percent accurate) definition of these interrelationships (set point) would require multiple measurements. Based on these same variations, to be significant at the 5 percent level the measured serum TSH concentration would need to change on average by 0.75 mU/L, and the respective changes in serum T_4 and T_3 concentrations and serum free T_4 index values would need to be 2.2 µg/dL (28 nmol/L), 37 ng/dL (0.55 nmol/L), and 2.6 (33).

Conclusion Serum TSH, T_4, and T_3 concentrations and serum free T_4 index values vary substantially from month to month in individual normal subjects and even more so between normal subjects.

COMMENTARY

These are important results. First, they highlight how much serum TSH and thyroid hormone values need to change to be confident there has been a change. This includes the man with subclinical hyperthyroidism; his serum T_4 and T_3 concentrations, while relatively high, varied as much about their mean values as did the values in the other men, although his serum TSH concentrations were ≤0.01 mU/L at all times. Only relatively young men were studied, at a time of day when the values change little (seasonal variations, described in some studies [1], were not mentioned). The results would probably be similar in women, but the between-subject variation would probably be greater in older subjects, especially women.

Second, the results help to explain why some patients with hypothyroidism or hyperthyroidism, whether overt or subclinical, have symptoms or other manifestations of thyroid dysfunction, for example hypercholesterolemia, and other patients do not. These disorders are defined in purely biochemical terms, which does not take into the account that some patients may have a very substantial change in serum thyroid hormone concentrations yet have subclinical hypothyroidism or subclinical hyperthyroidism, and others may have small changes yet have overt hypothyroidism or hyperthyroidism. It all depends on where they started, meaning their set point for TSH secretion.

Robert D. Utiger, M.D.

References

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Patients with hyperthyroidism caused by Graves' disease who have hypofunctioning thyroid nodules should be evaluated for thyroid carcinoma

Stocker DJ, Foster SS, Solomon BL, Shriver CD, Burch HB. Thyroid cancer yield in patients with Graves' disease selected for surgery on the basis of cold scintiscan defects. Thyroid 2002;12:305-11.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease may also have a thyroid nodule, and the proportion of nodules that are carcinomas may be higher in these patients than in otherwise normal subjects. This study was done to determine the clinical characteristics and, when available, pathologic findings in patients with Graves' hyperthyroidism who had hypofunctioning ("cold") thyroid nodules as detected by scintigraphy.

Methods The records of all 772 patients with hyperthyroidism caused by Graves' disease seen at the Walter Reed Army Medical Center from 1990 to the present were reviewed. Graves' disease was defined as hyperthyroidism and a high 24-hour thyroid radioiodine uptake or a positive test for thyrotropin (TSH) receptor-stimulating antibodies. Patients were excluded if the diagnosis of Graves' hyperthyroidism was uncertain, scintigraphy was not done or was done elsewhere, or management was not described.

The records of the remaining patients were reviewed in detail. Information collected included demographic data; estimated duration of hyperthyroidism; findings on physical examination; results of scintigraphy and other tests, including pathology; and management. Patients were considered to have cold nodules if their scan showed one or more discrete areas of low radionuclide (pertechnetate or iodine) uptake. Patients in whom the scan showed diffuse or patchy defects were excluded. The results in patients with scan defects were compared with the results in age- and sex-matched patients who had no scan defects.

Results Among the 772 patients, 447 (58 percent) were excluded, most often because the patient had initially been evaluated elsewhere. Among the remaining 325 patients, 39 (12 percent) had a focal scan defect. Subsequent evaluation by directed physical examination, ultrasonography, or repeat scintigraphy revealed no nodule in 11 of these 39 patients (28 percent). Six patients (15 percent) had a fine-needle aspiration biopsy that revealed benign thyroid follicular cells. These 17 patients were followed for 8 to 264 months (median, 21); apparently none had enlargement of their nodule during follow-up.

The remaining 22 patients had surgery, which revealed papillary carcinoma in 6 patients (15 percent of the patients with cold defects) (only 2 had biopsies, both of which revealed carcinoma), a benign nodule in 14 patients (4 had biopsies, which revealed benign cells in all), and no nodule in 2 patients. Three of the patients with carcinoma had recurrences within two years after initial surgery.

There were no differences in the mean age, numbers of women and men, duration of hyperthyroidism, goiter size, 24-hour thyroid radioiodine uptake values, or positive tests for TSH receptor-stimulating antibodies in the patients with cold defects and the matched control patients. Sixteen of the patients with cold defects, including two of the six patients with a carcinoma, but none of the control patients, had a palpable nodule.

Conclusion Thyroid scintigraphy in patients with Graves' hyperthyroidism may reveal hypofunctioning thyroid nodules, some of which are thyroid carcinomas.

COMMENTARY

There is some evidence that the frequency of thyroid carcinoma is increased in patients with hyperthyroidism caused by Graves' disease (summarized in ref. 1), but the increase may well be due to selection bias. Patients with Graves' hyperthyroidism are more likely to have more thorough palpation of their thyroid gland, more likely to have thyroid scintigraphy or ultrasonography, and even today may be more likely to have thyroid surgery and therefore pathologic examination of their thyroid, than most other patients. Once a nodule is detected in a patient with Graves' hyperthyroidism, the concern that it may be a carcinoma is heightened by suggestions that thyroid carcinoma may be more aggressive in these patients than in other patients (1).

Should all patients with Graves' hyperthyroidism have thyroid scintigraphy or ultrasonography to look for a thyroid carcinoma, or is physical examination adequate? Physical examination is adequate, for several reasons. One, there is no compelling evidence that the frequency or course of thyroid carcinoma is different in these than in other patients with thyroid carcinoma. Two, any nodules detected by imaging but not physical examination are likely to be small incidentalomas, and even if they prove in time to be carcinomas the patients have an excellent prognosis. Three, there are the hazards of additional testing and unnecessary surgery in patients with incidentalomas that are not carcinomas.

Robert D. Utiger, M.D.

References

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Color-flow Doppler sonography may help to distinguish between iodine-induced and thyroiditis-induced hyperthyroidism in patients treated with amiodarone

Eaton SE, Euinton HA, Newman CM, Weetman AP, Bennet WM. Clinical experience of amiodarone-induced thyrotoxicosis over a 3-year period: role of colour-flow Doppler sonography. Clin Endocrinol 2002;56:33-8.

SUMMARY

Background Amiodarone is an iodine-rich antiarrhythmic drug that can cause hypothyroidism and hyperthyroidism. The latter occurs as iodine-associated hyperthyroidism, usually in patients with a preexisting nodular goiter, and thyroiditis-associated hyperthyroidism, usually in patients with no preexisting thyroid disease. The usual treatment is an antithyroid drug for the former and an antithyroid drug and a glucocorticoid for the latter. This retrospective case study evaluated the role of color-flow Doppler ultrasonography for distinguishing between the two types of hyperthyroidism and the course of hyperthyroidism in untreated and treated patients.

Methods The study subjects were 37 patients (10 women and 27 men; mean age, 65 years [range, 20 to 86]) found to have amiodarone-associated hyperthyroidism at the Northern General Hospital in Sheffield, United Kingdom, from 1998 to 2000. The patients were identified because serum TSH was measured before and every six months during therapy in all patients given amiodarone; no patient was suspected to have hyperthyroidism before the measurement. Amiodarone-associated hyperthyroidism was defined as an undetectable serum thyrotropin (TSH) concentration (<0.03 mU/L) and a high serum free thyroxine (T_4) concentration in a patient who was taking amiodarone or who had taken it in the preceding year. In most patients, thyroid size was determined by two-dimensional ultrasonography, and thyroid vascularity by color-flow Doppler ultrasonography. Patients were considered to have iodine-associated hyperthyroidism if their thyroid gland was large and hypervascular, and thyroiditis-associated hyperthyroidism if the size was normal and vascularity was normal, patchy or reduced. Serum interleukin-6 and antithyroid peroxidase antibodies were measured in most patients. Treatment decisions were made on an individual basis.

Results The hyperthyroidism subsided spontaneously in seven patients. Based on the results of color-flow ultrasonography, two were thought to have iodine-induced hyperthyroidism and one thyroiditis-associated hyperthyroidism; and the results were equivocal in two. Amiodarone was discontinued in three patients.

Among the 30 patients who were treated, 25 underwent color-flow ultrasonography. Ten were thought to have iodine-associated hyperthyroidism and 10 thyroiditis-associated hyperthyroidism (Table); the results were equivocal in 5 patients. Serum antithyroid peroxidase concentrations were normal in all 25 patients. Five other patients were thought on clinical grounds to have iodine-associated hyperthyroidism.

Table. Characteristics of Patients Taking Amiodarone with Iodine- or Thyroiditis-Associated Hyperthyroidism.

	Iodine-Associated (N=10)	Thyroiditis-Associated (N=10)
Age (yr)	75 (49-85)	61 (20-86)
Men/women	4/6	9/1
Cumulative dose of amiodarone (g)	66 (13-188)*	186 (8-276)*
High serum interleukin-6 value	2	0
Serum free T_4 (ng/dL)**	4.0 (2.6-8.6)	5.8 (2.0-8.7)
Serum free T_3 (ng/dL)**	0.6 (0.5-1.0)*	1.0 (0.3-2.1)*

Values in parenthesis are ranges.
*P<0.05.
**Upper limit of normal range for serum free T_4 and free T_3 concentrations, 2.2 and 0.5 ng/dL, respectively. To convert serum free T_4 and free T_3 values to pmol/L, multiply by 12.9 and 0.015, respectively.

Among these 30 patients, 18 initially received carbimazole and prednisolone and 12 carbimazole alone (prednisolone was added later in 4). Amiodarone was discontinued in 26 patients. Five patients died, 4 while still hyperthyroid. All the other patients ultimately became euthyroid, although 2 required thyroidectomy. The duration of hyperthyroidism, the total duration of treatment (approximately 200 days), and the total doses of carbimazole were similar in the patients with the two types of hyperthyroidism, but the total dose of prednisolone was lower (mean, 0.6 vs. 2.8 g) and the duration of prednisolone therapy was shorter (mean, 30 vs. 91 days) in the patients with iodine-associated hyperthyroidism (mean, 0.6 vs. 2.8 g). No patient had recurrent hyperthyroidism after cessation of therapy.

Conclusion In patients with amiodarone-associated hyperthyroidism, color-flow Doppler sonography can help to distinguish between iodine-associated and thyroiditis-associated hyperthyroidism, and therefore potentially allow more specific therapy.

An antithyroid drug is effective therapy for most patients with amiodarone-associated hyperthyroidism

Osman F, Franklyn JA, Sheppard MC, Gammage MD. Successful treatment of amiodarone-induced thyrotoxicosis. Circulation 2002;105:1275-7.

SUMMARY

Background Treatment of patients with amiodarone-associated hyperthyroidism is difficult, because the drug causes two types of hyperthyroidism (iodine-associated and thyroiditis-associated hyperthyroidism), which are thought to require different treatment. This study was done to determine if patients with either type of hyperthyroidism respond to antithyroid drug therapy and whether the cessation of amiodarone therapy affects outcome.

Methods The study subjects were all 28 patients with amiodarone-associated hyperthyroidism seen at the Thyroid Clinic at the Queen Elizabeth Hospital, Birmingham, United Kingdom, in the preceding decade. There were 4 women and 24 men, with a median age of 64 years. The diagnosis was based on a low serum thyrotropin (TSH) concentration and high serum free thyroxine (T_4) and free triiodothyronine (T_3) concentrations. Patients with nodular goiter, or diffuse goiter or other features of Graves' disease, including high serum antithyroid peroxidase antibody concentrations, were categorized as having iodine-associated hyperthyroidism, and those with none of these findings were categorized as having thyroiditis-associated hyperthyroidism.

Results The indications for amiodarone therapy were ventricular tachycardia in 14 patients and atrial arrhythmias in 14 patients. Fifteen patients had ischemic heart disease, six had valvular heart disease, and seven had other cardiac disorders. The most common symptoms of hyperthyroidism were weight loss and worsening palpitations. Serum TSH concentrations were undetectable (<0.1 mU/L) in all patients; their median serum free T_4 and free T_3 concentrations were 3.7 ng/dL (48 pmol/L) and 0.5 ng/dL (8.2 pmol/L), respectively. Amiodarone was continued in 17 patients, including 12 of the patients with ventricular tachycardia.

In 5 patients, 4 of whom continued amiodarone, hyperthyroidism resolved spontaneously in a median interval of 3 months (interquartile range, 3 to 5 months). The other 23 patients were treated with carbimazole, 20 to 40 mg daily, and all became euthyroid (median interval, 5 months [interquartile range, 3 to 7]). Eleven patients remained euthyroid for a prolonged period (time not stated); carbimazole was continued in 5 and stopped in 6. Three patients developed hypothyroidism that persisted after carbimazole was stopped. Four patients became intolerant of carbimazole and were treated with propylthiouracil. Five patients treated with carbimazole relapsed after it was stopped; 3 responded to a second course and remained euthyroid, and 2 were given radioiodine after amiodarone was stopped. The total dose of carbimazole and the rate of improvement in thyroid function were similar in the patients in whom amiodarone was stopped and those in whom it was continued.

Fourteen patients (4 women and 10 men) were considered to have iodine-associated hyperthyroidism and 12 patients (all men) thyroiditis-associated hyperthyroidism. Between these two groups, there were no differences in the duration of amiodarone therapy before the onset of hyperthyroidism, the cumulative dose of amiodarone, or the cumulative dose of carbimazole needed to achieve euthyroidism.

Conclusion Among patients who have hyperthyroidism while receiving amiodarone, antithyroid drug therapy is equally effective in those with iodine-associated and those with thyroiditis-associated hyperthyroidism.

COMMENTARY

Amiodarone-associated hyperthyroidism is a difficult disorder to define and treat. Many patients have few symptoms, their hyperthyroidism is mild, or any symptoms of hyperthyroidism are overshadowed by those of their cardiac disorder or are minimized because they are also taking a beta-adrenergic antagonist drug. Therefore, the diagnosis of hyperthyroidism is based primarily on a low serum TSH concentration. Serum T_4 concentrations may be only minimally elevated, and serum T_3 concentrations may be normal, because amiodarone inhibits the extrathyroidal conversion of T_4 to T_3.

The two types of amiodarone-associated hyperthyroidism are reasonably well defined on paper, but the distinction between them rests primarily on the presence or absence of both goiter and hypervascularity, and some, perhaps many, patients do not meet the criteria for either type. Furthermore, the presumption that the type of hyperthyroidism determines treatment is not supported well by either of these studies. Eaton et al. state that the type of hyperthyroidism was a determinant of the type of treatment and its efficacy, but do not provide detailed data to support the statement. Osman et al. treated all their patients with an antithyroid drug, with good results in most patients. A substantial proportion of patients in both studies improved without any treatment, and it seems likely that many of those who were treated might have improved without treatment, especially if they had thyroiditis. The problem is that it is difficult to withhold antithyroid treatment in patients with cardiac disease who have biochemical, much less clinical, hyperthyroidism. Until amiodarone-associated hyperthyroidism is better understood, it seems appropriate to give an antithyroid drug, but adding a glucocorticoid is more problematic, and if Osman et al. are correct, it is not necessary.

Robert D. Utiger, M.D.

Hepatic disorders in patients with hyperthyroidism treated with methimazole or carbimazole

Woeber KA. Methimazole-induced hepatotoxicity. Endocr Pract 2002;8:222-4.

SUMMARY

Background All three antithyroid drugs in wide use — methimazole, carbimazole (which is rapidly converted to methimazole), and propylthiouracil — can cause hepatic disorders. This paper describes a patient with hyperthyroidism who had cholestatic hepatitis during treatment with methimazole and summarizes the findings in previously reported patients with hepatic disorders during treatment with methimazole or carbimazole.

Case Report A 36-year-old woman with a three-month history of symptoms and signs of hyperthyroidism, including decreased appetite, muscle weakness, and tremor, caused by Graves' disease, was treated with propranolol, 20 mg three times daily, and methimazole, 20 mg twice daily. At base-line, she had a diffuse goiter, no ophthalmopathy, and no hepatomegaly; laboratory results are shown in Table 1.

Table 1. Serum Free Thyroxine, Bilirubin, Alanine Aminotransferase, and Alkaline Phosphatase Concentrations in a Patient with Methimazole-Associated Cholestatic Hepatitis.

Day after Start of Methimazole	Free Thyroxine (ng/dL)*	Bilirubin (mg/dL)*	Alanine Aminotransferase (U/L)	Alkaline Phosphatase (U/L)
0	>5.5	1.1	47	113
23**	4.1	12.1	127	265
30	5.3	25.8	180	299
41	2.3	8.3	148	243
86	0.8	0.9	58	243
111**	0.4	0.5	61	263
Normal values	0.7-1.9	0.1-1.0	9-50	36-122

*To convert free thyroxine values to pmol/L, multiply by 12.9, and to convert bilirubin values to μmol/L, multiply by 17.1.
**Methimazole discontinued on day 19, and thyroxine started on day 111.

On day 19, she developed pruritus, jaundice, abdominal discomfort, and dark urine; methimazole was discontinued. On day 23, physical examination revealed jaundice, but no abdominal tenderness or hepatomegaly. Serologic studies for hepatitis A, B, and C were negative. Abdominal ultrasonography revealed intrahepatic cholestasis. The dose of propranolol was doubled, and she was given 15 mCi (555 MBq) radioiodine on day 27. Her liver function initially worsened, but then gradually improved (serum alkaline phosphatase was normal on day 207).

Review of Reported Cases Thirty-one patients, including this patient, with hepatic disorders while taking methimazole or carbimazole have been reported (Table 2). Among the 20 patients with cholestatic hepatitis, there were 14 women and 6 men, mean age 54 years (range, 24 to 81). The mean time of onset after starting treatment was 36 days (range, 12 to 90), and the mean daily dose of the drugs was 44 mg (range, 15 to 80). In most patients recovery was slow, but complete, as in this patient.

Table 2. Hepatic Disorders in Patients with Hyperthyroidism Treated with Methimazole or Carbimazole.

	Methimazole	Carbimazole
Cholestatic hepatitis	15	5
Toxic hepatitis	3*	2
Granulomatous hepatitis	1	1
Steatosis	1	0
Not known	3	0

*Two deaths.

Conclusion Methimazole and carbimazole occasionally cause cholestatic hepatitis or other hepatic disorders.

COMMENTARY

This case report and review serves as a reminder that methimazole and carbimazole can cause cholestatic hepatitis, fortunately usually transient. The 20 patients who had cholestatic hepatitis were receiving rather high doses of drug, which are not much more rapidly effective than lower doses (1), and are not necessary in most patients. The other liver disorders are so rare that a cause and effect relationship can be questioned.

Not only methimazole and carbimazole, but also propylthiouracil, is associated with hepatic injury, but the relative frequency is not known. A 1997 review identified 29 cases of propylthiouracil-associated toxic hepatitis (2), but in a systematic study of 497 patients treated with propylthiouracil, 1.2 percent had symptomatic hepatitis and 14 percent had transient asymptomatic increases in serum alanine aminotransferase concentrations (3). A systematic study of hepatic function in patients treated with methimazole or carbimazole has not been done.

Should liver function be assessed periodically in patients treated with an antithyroid drug? At present, this seems unnecessary, but certainly patients should be informed of the possibility of hepatic dysfunction.

Robert D. Utiger, M.D.

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3. Kim HJ, Kim BH, Han YS, et al. The incidence and clinical characteristics of symptomatic propylthiouracil-induced hepatic injury in patients with hyperthyroidism: a single-center retrospective study. Am J Gastroenterol 2001;96:165-9.

Localized dermopathy in Graves' disease changes little or resolves slowly with time, with or without topical glucocorticoid therapy

Schwartz KM, Fatourechi V, Ahmed DDF, Pond GR. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. J Clin Endocrinol Metab 2002;87:438-46.

SUMMARY

Background Localized dermopathy is a rare manifestation of Graves' disease, and relatively little is known about its pathogenesis and natural history. This study was undertaken to define the clinical characteristics, natural history, and effects of various treatments in a large group of patients with the disorder.

Methods The study subjects were 178 patients given a diagnosis of localized dermopathy at the Mayo Clinic between 1969 and 1995. The diagnosis was based on the presence of raised, waxy, sometimes indurated, skin lesions, varying in color from lighter to darker than the surrounding skin. The lesions were further categorized as nonpitting edema, plaque, nodular, and elephantiasic. Skin biopsies, done in 62 percent of the patients, revealed mucin deposition in the dermis in all patients, and lymphocytic infiltration in many of them. Treatment varied from none to topical glucocorticoid therapy covered by an occlusive dressing, applied one to three times daily, usually for two to ten weeks; a few patients were treated with subcutaneous injections of glucocorticoids or compressive dressings.

To determine outcome the patients' records were reviewed, and in 2000 they were sent a questionnaire asking about any treatment for their skin or thyroid after their last visit to the clinic and their current status. Among the 178 patients, 110 (62 percent) responded and 40 (22 percent) had died. The mean follow-up period was 8 years (range, 0 to 30). Outcome was categorized as complete remission (the absence of skin lesions), moderate improvement (the flattening of a plaque or nodule or a decrease in edema), and minimal or no change, at the last time for which information was available.

Results There were 142 women (80 percent) and 36 men (20 percent). At the time of diagnosis of dermopathy their mean age was 53 years (range 14 to 80); 162 (91 percent) had hyperthyroidism, 11 (6 percent) had hypothyroidism (4 had hyperthyroidism later), and 5 (3 percent) had normal thyroid function. One hundred seventy-one patients (96 percent) received one or more doses of iodine-131, 27 patients (15 percent) underwent thyroidectomy, and 43 patients (24 percent) received antithyroid drug therapy. In 148 patients (83 percent), thyroid disease preceded dermopathy. All 178 patients had ophthalmopathy, which usually preceded dermopathy, and 31 (17 percent) had thyroid acropachy.

The skin lesions were located in the pretibial region in 175 patients (98 percent), of whom 7 also had foot lesions and 2 had arm lesions. The lesions consisted of nonpitting edema in 77 patients (43 percent), plaques in 48 patients (27 percent), nodular lesions in 33 (18 percent), and elephantiasis in 5 patients (3 percent); the lesions were not defined in 15 patients (8 percent).

Ninety-six patients (54 percent) were treated with one or more courses of topical glucocorticoids, and 82 (46 percent) were not treated. The base-line characteristics of the patients, including the types of skin lesions, in these two groups were similar, except that all five patients with elephantiasis were treated. Of the 96 treated patients, 50 (52 percent) had minimal or no improvement, 26 (27 percent) had moderate improvement, and 20 (21 percent) had complete remission. Based on Kaplan-Meier estimates, 50 percent of the treated patients had a partial or complete remission by 17 years, as compared with 60 percent of the untreated patients. Overall, 46 patients (26 percent) had a complete remission (mean time, 9 years), 43 (24 percent) had moderate improvement, and 89 (50 percent) had little or no improvement.

Conclusion Nearly all patients with Graves' disease who have localized dermopathy have thyroid disease and ophthalmopathy. The dermopathy resolves slowly or not at all, and the benefit of topical glucocorticoid therapy is limited.

COMMENTARY

This paper contains a wealth of information, from the largest number of patients with localized dermopathy, and the longest follow-up, ever reported. Virtually all patients with dermopathy have severe Graves' disease, in that they have both hyperthyroidism and ophthalmopathy. Dermopathy is the last of the three components to appear.

The authors' classification of dermopathy into four types is reasonable for descriptive purposes, but distinguishing among them is not easy. The type of dermopathy was not a determinant of whether a patient received topical glucocorticoid therapy. As for this therapy, it wasn't effective, as compared with no therapy, although the authors suggest that the treated patients had more severe dermopathy. That is likely to be true, but severity was not assessed (it would not be easy) and the criteria for treatment are not described. It is likely that patients with dermopathy will continue to be treated with topical glucocorticoids, because that is the only treatment for which there are even hints of benefit, and it seems to be safe, even when applied daily in high doses under an occlusive dressing for many weeks or months (perhaps because no one has looked very carefully to determine if it isn't safe).

Robert D. Utiger, M.D.

Thyroxine therapy alone reverses hypertension in some patients with hypothyroidism

Dernellis J, Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. Am Heart J 2002;143:718-24.

SUMMARY

Background Patients with hypothyroidism have an increase is systemic vascular resistance, and some have hypertension that is reversible by thyroxine (T_4) therapy alone. This study evaluated the role of aortic stiffness in the pathogenesis of hypertension in patients with hypothyroidism, and the extent to which it decreased during treatment with T_4 and combined T_4 and calcium-channel antagonist drug therapy (felodipine).

Methods The main study group consisted of 30 patients (27 women, 13 men; mean [±SD] age, 44±12 years) with overt hypothyroidism (mean serum thyrotropin [TSH] concentration, 81 mU/L) and hypertension (mean blood pressure, 160±11/109±10 mm Hg). Other study groups (all age- and sex-matched) were 15 patients with hypothyroidism (mean serum TSH concentration, 81 mU/L) and normal blood pressure (mean, 121/86 mm Hg), 15 patients with hypertension (mean blood pressure, 155/108 mm Hg) and normal thyroid function, and 30 normal subjects (mean blood pressure, 125/78 mm Hg). None of the subjects had any evidence of coronary artery disease.

Blood pressure, systemic vascular resistance, and aortic stiffness were measured noninvasively at base line in all study subjects, after treatment with T_4 in the two groups of patients with hypothyroidism (mean duration, 9±2 months), after treatment with felodipine in the patients with hypertension, and also after the addition of felodipine in the 15 patients (50 percent) with hypothyroidism and hypertension who remained hypertensive (>140/90 mm Hg) during T_4 therapy (duration of felodipine therapy, six months). Aortic stiffness was calculated from measurements of blood pressure and aortic systolic and diastolic diameter measured 3 cm above the aortic valve.

Results As compared with the normal subjects, the patients with hypothyroidism and hypertension had a lower heart rate, higher aortic systolic and diastolic diameters, and increased aortic stiffness and systemic vascular resistance (all $P<0.01$). Also as compared with the normal subjects, the patients with hypothyroidism and normal blood pressure had a lower pulse rate, slightly higher diastolic blood pressure and aortic diastolic diameter, a slight increase in aortic stiffness, and increased systemic vascular resistance. The patients with hypertension also had increased aortic systolic and diastolic diameters, aortic stiffness, and systemic vascular resistance. The changes were for the most part reversible during T_4 or felodipine therapy, respectively, in the latter two groups.

Among the 30 patients with hypothyroidism and hypertension, 15 had normal blood pressure during T_4 therapy (mean blood pressure, 118/83 mm Hg). The other 15 patients had persistent hypertension during T_4 therapy (mean blood pressure, 151±105 mm Hg), and all 15 had normal blood pressure during felodipine therapy (mean, 114/83 mm Hg). The latter group had higher base-line values for aortic systolic and diastolic diameter, aortic stiffness, and systemic vascular resistance. Aortic stiffness and systemic vascular resistance decreased slightly during T_4 therapy in both groups, and decreased further during felodipine therapy, but not to normal in either group.

Among all treated patients, those with higher base-line values for aortic stiffness were less likely to have normalization of systolic blood pressure, and the decreases in systolic blood pressure during treatment were correlated with the decreases in aortic stiffness.

Conclusion Patients with hypothyroidism, especially those with hypertension, have increased aortic stiffness, both of which may be reversed by T_4 therapy.

COMMENTARY

To recapitulate, aortic stiffness and systemic vascular resistance were increased in all the patients with hypothyroidism, whether or not they had hypertension, and in patients with hypertension alone. The effect of the two disorders was additive Among the hypothyroid patients, half became normotensive with T_4 therapy alone. Not many patients with hypertension have hypothyroidism, but those who do should be treated with T_4 alone for a while.

Possible explanations for the increases in aortic stiffness and systemic vascular resistance in patients with hypothyroidism include atherosclerosis, associated with hypercholesterolemia and hyperhomocysteinemia; increased α-adrenergic stimulation, associated with increased serum norepinephrine concentrations and increased α-adrenergic receptors; and direct vasodilatory actions of thyroid hormone, in particular triiodothyronine. In support of the latter mechanisms, cessation of T_4 therapy for six weeks in patients with severe hypothyroidism resulted in mean increases of 5 and 10 mm in daytime systolic and diastolic blood pressures, respectively, and almost twofold increases in serum norepinephrine and epinephrine concentrations (1).

Robert D. Utiger, M.D.

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Lack of benefit of thyroxine therapy in patients with subclinical hypothyroidism

Kong WM, Sheikh MH, Lumb PJ, Freedman DB, Crook M, Doré CJ, Finer N. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Med 2002;112:348-54.

SUMMARY

Background Subclinical hypothyroidism is common, but whether patients with the disorder have symptoms and whether the symptoms improve with thyroxine (T_4) therapy are controversial. One reason for the varying responses to therapy may be the heterogeneity of the patients studied in the different trials. In this study a carefully selected group of patients was studied before and after T_4 therapy.

Methods The study subjects were 45 women (mean age, 49 years) who sought care for symptoms suggestive of hypothyroidism and who had serum thyrotropin (TSH) concentrations between 5 and 10 μU/mL and normal serum free T_4 concentrations (approximately 80 percent also had high serum antithyroid microsomal antibody concentrations). Women with a history of thyroid disease were excluded. The women were randomly assigned to receive 50 μg T_4 or placebo daily for six months. The dose of T_4 was doubled in 11 women who still had serum TSH values >5 μU/mL after treatment for three months, and the dose of placebo was similarly doubled in 11 women in the placebo group randomly selected by an independent physician.

Quality of life, hypothyroid symptoms, thyroid function, resting energy expenditure, and serum lipids were measured at base line and after T_4 therapy for three and six months. Quality of life was measured using the Hospital Anxiety and Depression Scale and the General Health Questionnaire, and hypothyroid symptoms were assessed using a score based on the presence or absence of seven common symptoms of hypothyroidism.

Results The base-line characteristics, including all questionnaire scores, the hypothyroid symptom score, and biochemical values, of the women in the two groups were similar. Twenty women in the T_4 therapy group and 15 women in the placebo group completed the study.

At six months, the mean serum free T_4 concentration increased by 0.2 ng/dL (2.6 pmol/L) and the mean serum TSH concentration decreased by 4.6 μU/ml in the T_4 therapy group, as compared with no change and a decrease of 1.7 μU/mL, respectively, in the placebo group (four women in this group had normal serum TSH concentrations then). The Hospital Anxiety and Depression scores and the General Health Questionnaire score did not change significantly in either group, nor did the proportions of women in whom the three scores improved, did not change, or worsened. For example, the depression score improved, did not change, or worsened in 65 percent, 25 percent, and 10 percent, respectively, of the women in the T_4 group, as compared with 64 percent, 7 percent, and 29 percent, respectively, in the placebo group ($P = 0.20$). The hypothyroid symptom score decreased to a similar extent in both groups, from 3.3 to 2.6 in the T_4 therapy group and from 3.8 to 2.5 in the placebo group; the symptoms that improved most often were fatigue, poor concentration, and dry skin or hair. There were no changes in body mass index, resting energy expenditure, or serum cholesterol, triglyceride, apoprotein A, or apoprotein B concentrations in either group.

Conclusion T_4 therapy for six months has no benefit in women with mild subclinical hypothyroidism.

COMMENTARY

This study has both strengths and weaknesses. The study subjects were all women, as are most patients with subclinical hypothyroidism, and they were carefully selected, in that they had only minimally elevated serum TSH concentrations. However, serum TSH apparently was measured only once, and therefore the elevation may have been a one-day event. In addition, the ranges of possible scores for the tests used to assess quality of life are not given, nor are results for these tests in age-matched normal women provided, so it is impossible to assess the extent to which the women's quality of life was impaired. Nonetheless, T_4 did not change anything.

These results will encourage those who think that patients with subclinical hypothyroidism should not be treated (1), but not discourage those who think that treatment is indicated (2). The former argue that many patients with slightly high serum TSH values do not have thyroid disease, just a mild and sometimes transient laboratory abnormality, and that in most placebo-controlled studies of patients with subclinical hypothyroidism, of which this is the sixth, T_4 therapy had few beneficial effects. The latter argue that some patients with subclinical hypothyroidism do benefit from T_4 therapy, and that subclinical hypothyroidism may have long-term risks (overt hypothyroidism, cardiovascular disease, central nervous system dysfunction), not measured in the clinical trials of therapy, none of which was longer than one year.

The everyday reality is that it is difficult not to treat these patients, given the possibility of benefit and the simplicity and safety of therapy. At the least, however, the patient should have a persistently high serum TSH concentration, and there should be some goal of treatment other than lowering the patient's serum TSH concentration to normal.

Robert D. Utiger, M.D.

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Thalidomide can cause hypothyroidism in patients with multiple myeloma

Badros AZ, Siegel E, Bodenner D, Zangari M, Zeldis J, Barlogie B, Tricot G. Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. Am J Med 2002;112:412-3.

SUMMARY

Background Thalidomide is an old drug, with very potent teratogenic properties, that recently has been found to have beneficial effects in several groups of patients, including patients with multiple myeloma, other tumors, erythema nodosum leprosum (the only approved use in the United States), aphthous stomatitis (in patients with HIV infection), chronic graft-versus-host disease, inflammatory bowel disease, and discoid lupus erythematosus. This article describes a patient with multiple myeloma who had hypothyroidism while receiving thalidomide, and the results of measurements of serum thyrotropin (TSH) in a large number of patients with multiple myeloma who where receiving thalidomide therapy.

Case Report The sentinel case was a 44-year-old man with multiple myeloma who had symptoms of hypothyroidism (cold intolerance, fatigue, depression, bradycardia) within four weeks after the initiation of thalidomide therapy (400 mg daily). His base-line serum TSH concentration was 2.6 μU/mL. His symptoms persisted after the dose of thalidomide was reduced to 200 mg daily. At three months, his serum TSH concentration was 115 μU/mL and his serum thyroxine (T_4) concentration was 1.8 μg/dL (23 nmol/L). He became euthyroid after T_4 was added.

Methods and Results Serum TSH was measured in two groups of patients. One group consisted of 174 patients with multiple myeloma who had been randomly assigned to receive chemotherapy and thalidomide, 400 mg daily, or chemotherapy alone. Serum TSH was measured three to four months after the initiation of these treatments. At this time, 18 of the 92 patients (20 percent) in the chemotherapy and thalidomide group had a serum TSH concentration >5 μU/mL, as compared with 7 of the 82 patients (9 percent) in the chemotherapy group. Six patients (7 percent) in the chemotherapy and thalidomide group, but none in the chemotherapy group, had a serum TSH concentration >10 μU/mL (range, 12 to 114; P = 0.01).

The second group consisted of 81 patients with multiple myeloma in relapse who had normal serum TSH concentrations. During treatment with 200 to 800 mg thalidomide daily for two to six months, their median serum TSH concentration increased by 48 percent (interquartile range, 0.1 to 103 percent; P<0.001). Eighteen patients (22 percent) had serum TSH concentrations >5 μU/mL, and 11 (14 percent) had concentrations ≥10 μU/mL.

Symptoms were not assessed and serum T_4 was not measured in either group of patients.

Conclusion Thalidomide has an antithyroid action in patients with multiple myeloma.

COMMENTARY

If these data are correct, thalidomide is a moderately potent antithyroid drug. By now, this drug has almost certainly been given for weeks or months to several thousand patients, with no mention of hypothyroidism. Could that be because thalidomide has an antithyroid action only in patients with multiple myeloma? That seems unlikely. More likely, it is because the drug reduces thyroid secretion only enough to cause subclinical hyperthyroidism, and most patients have no, or not enough, symptoms of hypothyroidism to warrant assessment of thyroid function. In addition, the hypothyroidism may be transient, thyroid secretion being restored to normal (or near normal) by the increase in TSH secretion.

Does thalidomide inhibit thyroid hormone synthesis, like methimazole or propylthiouracil, or does it induce painless (autoimmune) thyroiditis? Its structure is quite different from that of the two antithyroid drugs, but that hardly proves it does not act as an antithyroid drug. Its beneficial actions in some of the disorders listed above are thought to be due to immunomodulatory actions, in particular a decrease in the production of tumor necrosis factor-α, which suggests that it would not initiate or exacerbate autoimmune thyroiditis in the way that interferon-α is thought to do. Besides, in the survey of patients with multiple myeloma treated with thalidomide, no patient had a low serum TSH concentration, whereas many patients with thyroiditis associated with interferon-α therapy do.

There are severe restrictions on the prescription of thalidomide because of its teratogenic actions, so few physicians will want to prescribe it. Nonetheless, it is being evaluated in patients with some rather common disorders, and, given the data reported by Badros et al., the possibility that it may be the cause in a patient found to have hypothyroidism should be kept in mind.

Robert D. Utiger, M.D.

Thyroxine therapy is not associated with an increase in hip fracture in women

Sheppard MC, Holder R, Franklyn JA. Levothyroxine treatment and occurance of fracture of the hip. Arch Intern Med 2002;162:338-43.

SUMMARY

Background Spontaneously occurring hyperthyroidism is a risk factor for osteoporosis and hip fracture. Whether thyroid hormone therapy is also a risk factor for these problems is less clear. This case-control study evaluated the frequency of hip fracture in patients treated with thyroid hormone and matched control patients.

Methods The study subjects were 23,183 patients treated with thyroid hormone for at least one year and 92,732 control patients. The patients were identified from the General Practice Research Database in the United Kingdom, which contains data on approximately 3,500,000 people in 500 primary care practices. Patients who were <16 years old or who had a history of hyperthyroidism or of treatment with an antithyroid drug were excluded. The study and control patients were matched for age, sex, and duration of registration with the same practice. Among the treated patients, 98.5 percent were taking thyroxine (T_4). Information about hip fracture; the dose and duration of T_4 therapy; the presence of other disorders; and treatment with drugs that affect bone metabolism, such as vitamin D and glucocorticoids, was obtained.

Results The mean dose of T_4 was 0.107 mg daily, and the mean duration of therapy was 3.1 years (range, 1 to 22). The mean (±SE) age of the patients in both the T_4-treatment and control groups was 65±15 years; 88 percent of the patients in both groups were women, and 66 percent were aged 60 years or older.

Among the 23,183 T_4-treated patients, 373 (1.6±0.1 percent) had sustained a hip fracture, as compared with 1340 of the 92,732 control patients (1.4±0.04 percent, P = 0.06). Among the patients aged 60 years or older, 2.3±0.1 percent of the T_4-treated patients and 2.1±0.05 percent of the control patients had sustained a hip fracture (P = 0.09). The fracture rate was similar in the T_4-treated and control women (1.7±0.1 vs. 1.6±0.04 percent, P = 0.22), but it was higher in the T_4-treated than in the control men (1.2±0.2 vs. 0.7±0.1 percent, P = 0.008). The mean T_4 dose was lower in the women than in the men (0.106 vs. 0.121 mg daily, P<0.001), but for both women and men the doses were similar in the fracture and no-fracture groups.

The T_4-treated women and men were more likely to have other conditions and to have received drugs that affect bone metabolism than the control women and men. These conditions were chronic renal disease, chronic liver disease, inflammatory bowel disease, diabetes mellitus, rheumatoid arthritis (women only), and hyperparathyroidism, and the drugs included both those that protect bone (thiazide diuretics, vitamin D, calcium, gonadal steroids) and those deleterious to bone (glucocorticoids, anticonvulsant drugs). Most of these conditions and drugs were more common in the patients in both the T_4-treatment and control groups who had a hip fracture, as compared with the patients in the respective groups who did not have a hip fracture.

Overall, after adjustment for other factors, T_4 therapy was not associated with hip fracture in women (odds ratio, 1.0, 95 percent confidence interval, 0.9 to 1.2, P = 0.60). T_4 therapy was associated with hip fracture in men (odds ratio, 1.7, 95 percent confidence interval, 1.1 to 2.6, P = 0.01), but there was no relationship between T_4 dose and hip fracture.

Conclusion Hip fracture in women is not associated with T_4 therapy, but it may be in men.

COMMENTARY

The finding of similar rates of hip fracture in the T_4-treated and control women in this study is reassuring, and it confirms other studies (1,2). It might be even more reassuring if information about thyroid disease had been provided. How many of the women had a history of hyperthyroidism? In one study T_4 therapy was associated with hip fracture, but not after adjustment for a history of hyperthyroidism (3).

Why was the rate of hip fracture higher in the T_4-treated men than in the control men? Among the T_4-treated patients, the mean dose of T_4 was little higher in the men than in the women. There is therefore no reason to believe that more men were overtreated, and among the men there was no correlation between the dose of T_4 and hip fracture. It is unlikely that many of the men with hip fracture had a history of hyperthyroidism. The explanation for the difference in men probably lies in unexamined co-morbidities and concomitant treatment with other drugs, but why these should differ in women and men is not clear.

Robert D. Utiger, M.D.

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Thyroxine requirements decrease after renal transplantation in hypothyroid patients with end-stage renal disease

Thomas MC, Mathew TH, Russ GR. Changes in thyroxine requirements in patients with hypothyroidism undergoing renal transplantation. Am J Kidney Dis 2002;39:354-7.

SUMMARY

Background The frequency of primary hypothyroidism may be increased in patients with end-stage renal disease. The increase may be caused by iodine excess, in which case the hypothyroidism might be ameliorated by renal transplantation. This study describes the effect of transplantation on thyroxine (T_4) requirements in hypothyroid patients with end-stage renal disease.

Case Report A 55-year-old woman with a six-year history of hypothyroidism had serum thyrotropin (TSH) concentrations within the normal range while taking 150 μg T_4 daily for six months preceding cadaveric renal transplantation. During the immediate posttransplant period she received cyclosporine, mycophenolate, diltiazem, and glucocorticoids (two high doses of 6-methylprednisolone and then daily oral prednisolone). Between 16 and 24 days posttransplant, she had the onset of restlessness, tremor, insomnia, and atrial fibrillation. Her serum TSH concentration was <0.01 mU/L, with a high serum triiodothyronine and a normal serum T_4 concentration. Her dose of T_4 was gradually reduced, with amelioration of her symptoms; six months after transplantation, when taking 25 μg of T_4 daily, her serum TSH concentration was 2.4 mU/L. The patient's transplant functioned well throughout this interval.

Methods From 1990 to 2000, 456 patients with end-stage renal disease underwent cadaveric renal transplantation at the Queen Elizabeth Hospital, Adelaide, Australia. Among them, 20 patients (4 percent), 12 women and 8 men (mean age, 43 years), also had hypothyroidism and were receiving T_4 therapy. In nine patients the hypothyroidism preceded and in 11 patients it followed the onset of end-stage renal disease and the need for hemodialysis. At the time of diagnosis of hypothyroidism, the patients' serum TSH concentrations ranged from 10.2 to 32.0 mU/L and their serum free T_4 concentrations ranged from <0.1 to 1.8 ng/dL (1.3 to 23.2 pmol/L) (normal values not given); two of the five patients tested had high serum antithyroid antibody concentrations. The patients had been treated with T_4 for 1 to 10 years before renal transplantation. The data on T_4 doses were obtained by review of the patients' records before and after transplantation.

Results The dose of T_4 was reduced in all 20 patients in the first months after transplantation. At the time of transplantation, while being treated with dialysis, the patients' mean (±SD) dose of T_4 was 137±27 μg daily; six months after transplantation it was 61±12 μg daily. Before transplantation, the doses of T_4 ranged from 50 to 200 μg daily, whereas after it the doses ranged from 25 to 100 μg daily (it was 50 μg daily or less in 12 patients [60 percent]). All the patients received cyclosporine and glucocorticoids (stopped by six months in 10 patients), 14 patients received mycophenolate, and 6 patients received azathioprine. The dose of T_4 later had to be increased in three patients who had to resume dialysis therapy.

Conclusion Patients with end-stage renal disease and hypothyroidism need lower doses of T_4 after renal transplantation.

COMMENTARY

That these patients had hypothyroidism seems clear; at diagnosis all had high serum TSH concentrations, and most had what would be considered low serum free T_4 concentrations in most laboratories. That they needed less T_4 after transplantation also seems clear, but the paper lacks important details that might strengthen this conclusion, and perhaps also provide some insight into the mechanism of the decrease in need for T_4. For example, what were the causes of hypothyroidism? What were the patients' serum TSH and free T_4 concentrations at different times after transplantation? What criteria were used to alter the dose of T_4?

Possible explanations for a decrease in the need for T_4 after transplantation include improved T_4 absorption, slowed T_4 clearance, and an increase in endogenous T_4 production. Cessation of phosphate-binding therapy after transplantation could result in an increase in T_4 absorption. Iodide clearance increases after transplantation, which could result in an increase in T_4 production, particularly in patients who are sensitive to the antithyroid actions of iodide, such as patients with chronic autoimmune thyroiditis (1). In these same patients, T_4 production might also increase because of suppression of the autoimmune process by the posttransplant immunosuppressive therapy.

Robert D. Utiger, M.D.

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Screening for primary hyperparathyroidism and parathyroid incidentalomas in patients undergoing thyroid surgery

Denizot A, Dadoun F, Meyer-Dutour A, Alliot P, Argeme M. Screening for primary hyperparathyroidism before thyroid surgery: a prospective study. Surgery 2002;131:264-9.

SUMMARY

Background Patients with thyroid disorders may also have primary hyperparathyroidism. The hyperparathyroidism may be identified preoperatively, but more often it is discovered by the chance detection of a parathyroid adenoma during thyroid surgery. This prospective study was done to evaluate the utility of screening for primary hyperparathyroidism in patients needing thyroid surgery.

Methods All 748 patients (611 women and 137 men; mean age, 48 years) referred to one surgeon for thyroid surgery during a two-year period were screened for primary hyperparathyroidism by measurement of serum calcium at the time of their initial evaluation. Patients with serum calcium concentrations <10 mg/dL (2.5 mmol/L) were not studied further (normal range for serum calcium, 8.8 to 10.4 mg/dL [2.2 to 2.6 mmol/L]). In those patients with a serum calcium concentration ≥10.0 mg/dL (2.5 mmol/L), serum calcium and parathyroid hormone (PTH) were measured. Positive screening was defined as two serum calcium values ≥10.0 mg/dL (2.5 mmol/L) and a serum PTH value ≥50 pg/mL (normal range, 10 to 65).

The surgeon knew the results of the screening studies. In the patients who had a serum calcium concentration <10 mg/dL (2.5 mmol/L), the surgeon looked for the parathyroid glands near the thyroid, but did not look further if parathyroid glands were not seen. If an enlarged parathyroid gland was seen, other parathyroid glands were examined, and all enlarged parathyroid glands were resected. In patients in the positive screening group, the surgeon looked for four parathyroid glands before removing any thyroid tissue. Parathyroid adenomas found near a thyroid lesion were rated easily accessible, and all others were rated as requiring specific dissection.

Results Among the 748 patients, 246 (33 percent) had a thyroid nodule, 207 (28 percent) a toxic goiter, 288 (38 percent) a nontoxic multinodular goiter, and 7 (1 percent) sporadic medullary carcinoma. Eighty-seven patients (12 percent) had an initial serum calcium concentration ≥10.0 mg/dL (2.5 mmol/L). Among them, 30 had a repeat serum calcium concentration ≥10.0 mg/dL (2.5 mmol/L). Nine (30 percent) of these 30 patients had a serum PTH concentration ≥50 pg/mL (positive screening group); the remainder had values ranging from <20 to 41 pg/mL.

At surgery, all 9 patients in the positive screening group were found to have a parathyroid adenoma (weight, 100 to 1000 mg). The adenoma was rated as easily accessible in 6 patients and requiring specific dissection in 3 patients. Among the 739 patients in whom screening was negative, 12 (2 percent) had one or more visibly enlarged parathyroid glands, which were resected (weight, 100 to 400 mg). One day after surgery, serum calcium concentrations were normal or low in 746 patients and high in 2 patients (both in the negative screening group); both patients later had high serum calcium and PTH values.

Overall, 23 of the 748 patients (3 percent) had parathyroid disease; 12 (2 percent) had incidentalomas discovered at surgery, 9 (1 percent) had parathyroid adenomas detected by screening, and 2 patients (0.3 percent) were found to have hyperparathyroidism after thyroid surgery.

Conclusion Screening patients scheduled for thyroid surgery for primary hyperparathyroidism results in the detection of a few patients in whom the abnormal parathyroid tissue is unlikely to be detected incidentally during surgery.

COMMENTARY

The authors suggest that only three patients benefited from screening—those found by screening to have primary hyperparathyroidism in whom the parathyroid adenoma was rated as requiring specific dissection. A few more patients may in fact have benefited, because it is not certain that the six adenomas rated as easily accessible would have been detected had the surgeon not known that the patient had primary hyperparathyroidism.

The parathyroid incidentalomas were an adenoma (rim of normal tissue seen) in 4 patients, a single hyperplastic gland (no rim of normal tissue) in 3 patients, two hyperplastic glands in 2 patients, and normal parathyroid tissue (despite weight ≥100 mg) in 3 patients. Whether any of these patients were among the 87 patients whose first serum calcium value was above the threshold for further testing, or any of them had conditions causing secondary hyperparathyroidism, is not stated. Given that most people have four (or more) parathyroid glands, it is reasonable to remove an enlarged parathyroid encountered incidentally during thyroid surgery.

Measuring serum calcium before thyroid surgery may also reveal hypocalcemia, leading to a diagnosis of hypoparathyroidism before, rather than after, surgery.

Robert D. Utiger, M.D.

Nearly all substernal goiters can be removed by standard thyroid operative procedures

Hedayati N, McHenry CR. The clinical presentation and operative management of nodular and diffuse substernal thyroid disease. Am Surg 2002;68:245-51.

SUMMARY

Background A substernal goiter refers to the presence of a substantial amount of thyroid tissue below the plane of the thoracic inlet. The substernal extension may be unilateral or bilateral, and may consist of benign or malignant thyroid tissue. This case study summarizes the findings in all patients found to have substernal thyroid disease at the time of surgery at a single hospital from 1990 to 2000.

Patients During the study period 381 patients underwent thyroidectomy, of whom 116 (30 percent) had substernal thyroid disease, defined intraoperatively as the extension of at least 3 cm of thyroid tissue from the neck below the plane of the thoracic inlet with the neck extended or the presence of all thyroid tissue in the chest. There were 95 women (82 percent) and 21 men (18 percent), with a mean age of 52 years (range 10 to 88). Thirteen patients had previously undergone thyroid surgery.

Results Some thyroid abnormality was present on physical examination in 94 patients (81 percent). Fine-needle aspiration biopsy, done in 99 patients, revealed benign thyroid cells in 42 patients, follicular tumor in 27, and carcinoma or suspicion of carcinoma in 18, and was nondiagnostic in 12 patients. The indications for surgery were symptoms of compression of one or more neck structures in 75 patients (65 percent), including hoarseness in 40 patients, dysphagia in 37 patients, dyspnea in 34 patients, and cough in 7 patients; an abnormal biopsy in 45 patients (39 percent); progressive thyroid enlargement in 41 patients (35 percent); impingement on the trachea or esophagus, as detected by plain or barium x-rays or computed tomography, in 41 patients (35 percent); hyperthyroidism in 11 patients (9 percent); and superior vena cava obstruction in two patients (2 percent).

Thyroid tissue was resected through a standard collar incision in 114 patients. In the other two patients, both of whom had previously undergone surgery for multinodular goiter, all thyroid tissue was substernal, and both had thoracic operations. In 109 patients (94 percent), the substernal goiter was in the anterior mediastinum, and it was in the posterior mediastinum in 7 patients (6 percent). Total or near-total thyroidectomy was done in 75 patients (65 percent), lobectomy in 37 patients (32 percent), and biopsy in 4 patients (3 percent), with removal of an average of 108 g of thyroid tissue (range, 15 to 800). The pathologic diagnoses are shown in the Table.

Table. Pathologic Diagnoses in 116 Patients with Substernal Goiter.

	No, (%)
Carcinoma*	25 (22)
Benign	
Adenomatous goiter	68 (59)
Follicular adenoma	20 (17)
Thyroiditis	3 (2)

*Papillary carcinoma, 14; follicular carcinoma, 4: medullary carcinoma, lymphoma, and anaplastic carcinoma, 2 each; and Hurthle-cell carcinoma, 1.

In four patients with thyroid carcinoma the tumor was not resectable. One patient died during a mean follow-up period of 15 months.

Conclusion Both benign and malignant thyroid disease may be substernal, and nearly always can be removed in conjunction with cervical thyroid tissue by standard thyroid operative procedures.

COMMENTARY

The frequency of substernal goiter among patients with thyroid disease varies substantially, even among patients who undergo surgery, because the definition of substernal goiter varies, for example, from that there be modest extension of thyroid tissue from the neck into the thorax, as in this paper, to that more than 50 percent of thyroid tissue be below the thoracic inlet. The authors' rather nonstringent definition explains the high frequency (30 percent) of substernal goiter among their patients who underwent thyroidectomy, and it also explains why the abnormal thyroid tissue could be removed through a standard neck incision in nearly all the patients. Note that up to 800 g of thyroid could be removed in this way, although in all likelihood most of the thyroid tissue in the patients with very large goiters was in the neck.

The percentage of patients who had symptoms of compression of the trachea or esophagus was substantial, and probably higher than would be present in patients with similar thyroid diseases confined to the neck. It seems clear that these symptoms will continue to be an important indication for thyroidectomy, including or perhaps especially in patients with a substernal goiter, despite the growing experience with radioiodine therapy as a means to decrease goiter size (slowly) and relieve the symptoms (also slowly) (1).

Robert D. Utiger, M.D.

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Breast milk contains too little thyroid hormone to raise plasma thyroid hormone concentrations in preterm infants

Van Wassenaer AG, Stulp MR, Valianpour F, Tamminga P, Ris Stalpers C, de Randamie JSE, van Beusekom C, de Vijlder JJM. The quantity of thyroid hormone in human milk is too low to influence plasma thyroid hormone levels in the very preterm infant. Clin Endocrinol 2002;56:621-7.

SUMMARY

Background Breast milk may contain small amounts of thyroxine (T_4) and triiodothyronine (T_3). The amounts are too low to raise plasma T_4 and T_3 concentrations in normal infants, but in some studies of preterm infants or infants with congenital hypothyroidism plasma T_4 and T_3 concentrations were higher in breast-fed than in formula-fed infants. In this study plasma T_4 and T_3 concentrations were measured in breast milk-fed and formula-fed preterm infants.

Methods The study subjects were preterm infants (gestational age, 25 to 30 weeks) who were part of the control group of a study of the effect of T_4 therapy on postnatal development. Infants with severe malformations or whose mothers had endocrine disorders or used illicit drugs were excluded. The infants were given decreasing amounts of parenteral feedings and increasing amounts of enteral feedings starting at birth; by two weeks most infants received only enteral feedings of expressed breast milk or formula, as desired by their mothers. The infants were divided into breast milk and formula-fed groups on the basis of the daily intake of breast milk in relation to total intake during the third, fourth, and fifth weeks of life. The breast milk group received >50 percent of their caloric intake as breast milk, and the formula group received <25 percent of their caloric intake as breast milk; infants who had intermediate breast milk intake were excluded.

Plasma T_4, free T_4, T_3, and thyrotropin (TSH) were measured on days 7, 14, 21, 28, 35, and 42 days after birth in all infants. In addition, T_4 and T_3 were measured in 119 samples of milk collected 1 to 10 weeks after delivery from 32 mothers of preterm infants, in one sample collected during the first week after delivery from 10 mothers of term infants, and in the formula used. T_4 and T_3 were extracted from breast milk and formula before assay.

Results There were 32 infants in the breast milk group and 25 infants in the formula group. There were no differences between the groups in gestational age at birth, birth weight (mean, approximately 1100 g), percentages of girls and boys, antenatal glucocorticoid exposure, surfactant therapy, sepsis, or bronchopulmonary dysplasia.

The mean plasma T_4, free T_4, and T_3 concentrations were almost identical at all six times in both groups. The approximate (the estimated mean of the values for both groups extrapolated from Figure 1 of the paper) plasma T_4 values were 5.0 μg/dL (65 nmol/L) at 7 days, 8.1 μg/dL (105 nmol/L) at 21 days, and 7.9 μg/dL (102 nmol/L) at 42 days. Plasma TSH concentrations also were similar in both groups at all times.

The concentrations of T_4 in the milk of the mothers of preterm infants ranged from 0.02 to 0.18 μg/dL (0.2 to 2.3 nmol/L). The mean (±SD) T4 concentration in the formula was 0.09±0.04 μg/dL (1.2±0.5 nmol/L). The breast milk T_3 concentrations averaged 14 ng/dL (0.2 nmol/L); T_3 was not measured in the formula. In the milk samples collected during the first week after birth, the mean T_4 concentrations were 0.09 μg/dL (1.2 nmol/L) in the samples from mothers of preterm infants and 0.50 μg/dL (6.4 nmol/L) in the samples from the mothers of term infants.

Conclusion Plasma T_4 and T_3 concentrations are similar in preterm infants fed breast milk and formula during the first weeks of life.

COMMENTARY

Plasma T_4 and T_3 concentrations fall transiently in preterm infants, even healthy preterm infants, reaching a nadir about seven days after birth. The concentrations then rise, as in these infants. The falls are attributed to both immaturity of the hypothalamic-pituitary-thyroid axis and nonthyroidal illness. Administering T_4 for the first 42 days of life to prevent the falls does not affect later development (1); the infants in this study were part of the placebo group in ref. 1. In contrast, in term infants the concentrations rise substantially in the first days after birth and then gradually fall.

The breast milk of the mothers of preterm infants contained no more T_4 than did the formula used, and the plasma T_4 and T_3 concentrations in the breast milk and formula-fed infants were similar. Furthermore, the authors calculated that the infants received a total of 0.11 to 0.14 μg of T_4 per kg daily from the milk, whereas in their treatment study they gave 8 μg of T_4 per kg daily to mimic the plasma concentrations in term infants (1). Indeed, the measured concentrations of T_4 and T_3 in milk were so low that one wonders if any T_4 was present. ^{125}I-T_4 was added to the milk (and presumably formula) before extraction, and the measured values were corrected for recovery of radioactivity, but not T_4 per se. While it is reasonable to suppose that some T_4 reaches breast milk from plasma, why should any infant formula contain T_4?

Robert D. Utiger, M.D.

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Nodular goiter is common in patients with acromegaly

Gasperi M, Martino E, Manetti L, Arosio M, Porretti S, Faglia G, Mariotti S, Colao AM, Lombardi G, Baldelli R, Camanni F, Liuzzi A, and the Acromegaly Study Group of the Italian Society of Endocrinology. Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multi-center study. J Endocrinol Invest 2002;25:240-5.

SUMMARY

Background Thyroid dysfunction and goiter are common in patients with acromegaly, but their frequency and relation to the duration and severity of the disease have not been evaluated extensively. This study was undertaken to determine the frequency of thyroid dysfunction and goiter in a large group of patients with acromegaly and patients with other pituitary tumors.

Methods The study subjects were 258 patients with acromegaly (147 women and 111 men; mean [±SD] age, 50±13 years) and 150 patients with other pituitary tumors (122 women and 28 men; mean age, 48±15 years) seen at nine centers in Italy. Among the latter patients, 106 had prolactinomas and 44 had nonsecreting tumors. All patients with acromegaly had active disease, as defined by a high serum insulin-like growth factor (IGF)-I concentration (for age) and a serum growth hormone (GH) concentration >2 ng/mL after glucose ingestion, although 88 (34 percent) had received some treatment. Two patients who had tumors that co-secreted thyrotropin (TSH) were excluded from the analysis. Eleven patients with acromegaly had undergone thyroid surgery, 21 were being treated with thyroxine (T_4), and 4 were being treated with methimazole. The patients lived in areas in which urinary iodine excretion ranged from 50 to 110 μg/L.

Thyroid volume was measured by ultrasonography. The scans were read by one person who was unaware of the patient's diagnosis. Goiter was defined as a thyroid volume >13 mL in women and >18 mL in men. Thyroid radionuclide imaging was done using pertechnetate-99m or iodine-131. Thyroid biopsies were done in 62 patients with acromegaly and 14 patients with other pituitary tumors. Serum free T_4, free triiodothyronine (T_3), TSH, antithyroid peroxidase and antithyroglobulin antibodies, GH, IGF-I, and prolactin were measured in all patients.

Results A thyroid abnormality was found in 202 (78 percent) of the patients with acromegaly, as compared with 41 (27 percent) of the patients with other pituitary tumors (P<0.01) (Table 1). The frequency of thyroid disorders was similar in women and men (81 vs. 77 percent) in the acromegaly group, but higher in women than men in the other pituitary tumor group (31 vs. 11 percent, P = 0.05).

Table 1. Frequency of Thyroid Disorders in Patients with Acromegaly or Other Pituitary Tumors.

	Nontoxic Nodular Goiter	Nontoxic Diffuse Goiter	Toxic Nodular Goiter	Toxic Diffuse Goiter	Hashimoto's Thyroiditis
Acromegaly	103 (40%	46 (18%)	37 (14%)	1 (0.4%)	12 (5%)
Other tumor	20 (13%)*	6 (4%)*	2 (1%)*	1 (0.7%)	11 (7%)

*P<0.01, as compared with the acromegaly group.

The mean thyroid volume in 194 patients with acromegaly who had not received treatment for a thyroid disorder was 24±17 mL (range, 4 to 137), as compared with 14±13 mL (range, 4 to 87) in the patients with other pituitary tumors (P<0.01). Thyroid volume was correlated with the estimated duration of acromegaly, but not with patient age, serum GH concentrations (mean, 25 ng/mL), or serum IGF-I concentrations (mean, 752 ng/mL). Serum thyroid hormone and TSH values are shown in Table 2.

Table 2. Mean (±SD) Serum Hormonal Values in Patients with Acromegaly or Other Pituitary Tumors.

	Serum Free T_4 (ng/dL)	Serum Free T_3 (ng/dL)	Serum TSH (mU/L)
Acromegaly (n = 222)*	1.2±0.5**	0.34±0.14**	1.1±1.0
Other tumors (n = 150)	1.0±0.3	0.32±0.08	1.3±1.0

*Excluding patients who received treatment for a thyroid disorder.
**To convert serum free T_4 and free T_3 values to pmol/L, multiply by 12.9 and 0.015, respectively.

Conclusion Thyroid disorders, in particular nontoxic nodular goiter, are common in patients with acromegaly.

COMMENTARY

It is not surprising that patients with acromegaly have thyroid enlargement, given that most of their other organs are enlarged. Is the enlargement caused by systemic or local production of IGF-I, the major mediator of the growth-promoting actions of GH, and why does it often take the form of a multinodular goiter? Thyroid tissue contains both GH receptors and IGF-I receptors, making it likely that locally produced IGF-I is as important as if not more important than systemically produced IGF-I as a cause of the thyroid enlargement in patients with acromegaly. Some TSH seems to be necessary as well, because GH does not increase thyroid size in patients with TSH deficiency (1).

The high frequency of nodular goiter in patients with acromegaly in this study probably resulted from marginal dietary iodine intake, itself a cause of nodular goiter, plus the growth-promoting actions of IGF-I in thyroid tissue. The formation of thyroid nodules seems to depend on a process of clonal selection, and it is not surprising that the process might be augmented by locally or systemically produced IGF-I. Some of the nodules must become TSH-independent, thereby explaining the occurrence of toxic multinodular goiter.

Robert D. Utiger, M.D.

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Production of thyrotropin receptor antibodies in patients with toxic nodular goiter treated with radioactive iodine

Wallaschofski H, Muller D, Georgi P, Paschke R. Induction of TSH-receptor antibodies in patients with toxic multinodular goiter by radioiodine treatment. Horm Metab Res 2002;34:36-9.

SUMMARY

Background Radioiodine (I-131) is an effective therapy for patients with hyperthyroidism caused by a thyroid adenoma or a multinodular goiter. In some patients, this therapy results in the production of thyroid antibodies. In this study several antithyroid antibodies were measured before and after I-131 therapy in patients with hyperthyroidism caused by a thyroid adenoma or multinodular goiter.

Methods The study subjects were 41 consecutive patients with hyperthyroidism caused by some type of thyroid nodular disease referred to a nuclear medicine clinic for I-131 therapy. Twenty of the patients had a solitary thyroid adenoma, and 21 patients had a multinodular goiter, as determined by scintigraphy with technetium-99m. Among the latter the pattern of uptake was diffuse but patchy or uneven in 11 patients and localized in multiple discrete nodules in 10 patients. All the patients had been treated with methimazole for at least six months (and presumably were euthyroid when treated with I-131). Serum antithyroid peroxidase antibodies, antithyroglobulin antibodies, and thyrotropin (TSH) receptor antibodies were measured before and 3 to 11 months after I-131 therapy. Serum TSH receptor antibodies were measured by their ability to inhibit the binding of TSH to its receptor, mimic the biological action of TSH in cells with TSH receptors, and inhibit the action of TSH in these cells.

Results Before I-131 therapy, none of the 41 patients had any of the three types of TSH receptor antibodies. After therapy, four patients, all in the group of 11 patients with a diffuse but patchy multinodular goiter, had a high serum concentration of TSH-binding inhibitory antibodies, but not the other two types of TSH receptor antibodies. Three of these four patients had a high serum antithyroid peroxidase antibody concentration before I-131 therapy; after therapy the concentrations increased in these three patients, and three other patients in this group had high concentrations. Two patients had high serum antithyroglobulin antibody concentrations before I-131 therapy, and they and one other patient had a high concentration after therapy.

Among the 10 patients with multiple discrete nodules, none had a high serum concentration of any of the antibodies before I-131 therapy, and one patient had a high serum antithyroid peroxidase antibody concentration after therapy. Among the 20 patients with a solitary thyroid adenoma, one had a high serum antithyroid peroxidase concentration before therapy, and it increased after therapy.

Conclusion Among patients with hyperthyroidism caused by a nodular goiter treated with I-131, serum TSH receptor antibody concentrations increased only in patients with a diffuse or patchy multinodular goiter, suggesting that these patients have preexisting Graves' disease.

COMMENTARY

Several aspects of this study are problematic. How clear is the difference between diffuse but patchy uptake and multiple discrete nodules? The conclusion that the 11 patients with diffuse but patchy uptake had preexisting Graves' disease was based not on clinical and laboratory findings at the time of diagnosis of hyperthyroidism, or indeed on the presence of high serum TSH receptor-stimulating antibody concentrations at any time, but on the basis of the scan results and also increases in serum antithyroid antibody concentrations after I-131 therapy in only a minority of the 11 patients. There is no reason why Graves' disease cannot occur in patients with a preexisting nodular goiter, and if it did it probably would cause the pattern of radionuclide uptake to be diffuse or patchy, but the latter finding and limited serologic findings do not provide a firm basis for a diagnosis of Graves' disease.

The clearest conclusion from this study is that I-131 therapy in patients with a toxic nodular goiter is occasionally followed by the production of antibodies to one or more components of thyroid tissue, especially in patients who have a high serum concentration of one or more antithyroid antibodies before therapy. Indeed, the proportion of patients with high serum antibody concentrations undoubtedly would have been higher had the measurements been done more often. Thyroid injury induced by I-131 is not unique in this regard; other types of thyroid injury, for example surgery and subacute granulomatous (painful) thyroiditis, also are followed in some patients by high serum antithyroid antibody, including TSH receptor antibody, concentrations. In most patients the thyroid injury does not result in sustained antibody production or persistent thyroid disease. Even if TSH receptor antibody production is sustained, the thyroid gland may be so severely damaged that hyperthyroidism cannot occur. However, in a few patients with a toxic multinodular goiter, and also in a few patients with a nontoxic multinodular goiter, I-131 therapy has been followed by the production of TSH receptor antibodies and hyperthyroidism (1,2), and this possibility should be kept in mind when I-131 is given to patients with a multinodular goiter.

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Thyroid radioiodine scans have little value in patients with thyroid carcinoma who have undetectable stimulated serum thyroglobulin values after initial therapy

Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A. Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 2002;87:1499-5010.

SUMMARY

Background Most patients with thyroid carcinoma are treated by thyroidectomy and then iodine-131 (I-131), given primarily to destroy any remaining normal thyroid tissue. In the past, most patients had a diagnostic whole-body I-131 scan 6 to 12 months later, several weeks after withdrawal of thyroxine (T_4) therapy, to verify destruction of the thyroid remnant and detect persistent carcinoma. This retrospective study was done to determine if scanning at this time provided useful information in patients who had undetectable serum thyroglobulin concentrations after the withdrawal of T_4 therapy.

Methods The study subjects were 315 patients (261 women and 54 men; mean age, 41 years [range, 12 to 76]) with thyroid carcinoma who had undetectable (<3 ng/mL) serum thyroglobulin concentrations, and no detectable serum antithyroglobulin antibodies, after withdrawal of T_4 therapy, between 6 and 12 months after initial treatment. The carcinoma was a papillary carcinoma in 272 patients (86 percent) and a follicular carcinoma in 43 patients (14 percent). The carcinoma was limited to the thyroid gland in 195 patients (62 percent), involved cervical lymph nodes in 76 patients (24 percent), extended beyond the thyroid in 17 patients (5 percent), and was not classified in 27 (9 percent).

The initial treatment consisted of near-total thyroidectomy and administration of 30 to 100 mCi (1110 to 3700 MBq) of I-131. Whole-body scans after this treatment revealed uptake of I-131 in the thyroid bed of all patients; 33 patients (10 percent) also had uptake in cervical lymph nodes, and 4 patients (1 percent) had distant metastases. Six to 12 months later, T_4 was discontinued. Serum thyroglobulin was measured and a diagnostic whole-body I-131 scan was done when the patients' serum thyrotropin (TSH) concentration was >30 μU/mL. The scans were done two or three days after the administration of 4 to 5 mCi (148 to 185 MBq) of I-131. Thereafter, the patients were examined yearly and had periodic measurements of serum thyroglobulin before and after withdrawal of T_4 therapy and periodic diagnostic whole-body I-131 scans after withdrawal of T_4 therapy.

Results The diagnostic whole-body scan done 6 to 12 months after initial treatment in these 315 patients revealed no uptake in 225 patients (71 percent) and uptake in the thyroid bed in 90 patients (29 percent); no patient had any metastases. Among the 90 patients with uptake in the thyroid bed, 54 were given a second dose of I-131, 7 were given two doses, and 29 were not retreated.

During subsequent follow-up, which ranged from 9 to 19 years (mean, 12 years), 281 patients (89 percent) had persistently undetectable serum thyroglobulin concentrations and negative diagnostic whole-body I-131 scans, 29 patients (9 percent) had persistently undetectable serum thyroglobulin concentrations but I-131 uptake in the thyroid bed, and 2 patients (1 percent) had recurrent thyroid carcinoma (in cervical lymph nodes). Three patients (1 percent) died of other causes.

Conclusion Patients with thyroid carcinoma who have undetectable serum thyroglobulin concentrations after the withdrawal of T_4 therapy 6 to 12 months after initial surgery and I-131 therapy rarely have abnormal I-131 scans, and few later have recurrent carcinoma.

COMMENTARY

The results of this study demonstrate clearly that patients with very low serum thyroglobulin concentrations after the withdrawal of T_4 are very unlikely to have any uptake of I-131 (except in the thyroid bed in some patients). These results confirm those of an earlier study of 256 patients treated in the same way (1). After withdrawal of T_4 therapy serum thyroglobulin concentrations were undetectable in 82 percent, ranged from 1 to 10 ng/ml in 12 percent, and were >10 ng/mL in 6 percent. At that time, 92 percent of the patients had no uptake of I-131, and 8 percent had I-131 uptake in the thyroid bed; only 3 percent of patients had recurrent carcinoma later. Similarly, patients who have undetectable serum thyroglobulin concentrations after the administration of TSH rarely have an abnormal diagnostic whole-body scan (2).

It seems clear that diagnostic whole-body radioiodine scanning has little value, and the prognosis is excellent, in patients who have undetectable serum thyroglobulin concentrations when their serum TSH concentrations are high, whether the elevation is due to increased endogenous TSH secretion or exogenous TSH administration.

Robert D. Utiger, M.D.

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Fertility is not impaired after radioiodine therapy in women with thyroid carcinoma

Vini L, Hyer S, Al-Saadi A, Pratt B, Harmer C. Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer. Postgrad Med J 2002;78:92-3.

SUMMARY

Background Some women with thyroid cancer who are treated with high doses of iodine-131 (I-131) have transient impairment in ovarian function, but the extent to which fertility is impaired is uncertain. This study assessed the frequency of menstrual disturbances and pregnancies in a large group of women with thyroid cancer who had been treated with I-131.

Methods The study subjects were 496 women with thyroid cancer who were less than 40 years old at the time of diagnosis, were treated at a single center between 1949 and 1997, and survived for at least two years thereafter. All were treated with surgery and then one or mores doses of I-131. The women were asked about their menstrual and obstetric histories and their wishes for children at the time of follow-up visits or by mail.

The median age of the women at the time of diagnosis was 31 years (range, 8 to 40). Three hundred eighty-one women (77 percent) had a papillary carcinoma, and 115 (23 percent) a follicular carcinoma. In most of the women the tumor was confined to the thyroid gland, but it extended beyond the thyroid in 89 women (18 percent). After initial surgery, 322 women (65 percent) received a single dose of I-131 (30 mCi [1.1 GBq] or 80 mCi [3.0 GBq]); the remaining 174 women (35 percent) received additional doses (total dose, 230 to 1600 mCi [8.5 to 59 GBq]) because they had persistent or recurrent tumor. The women had been advised not to become pregnant for one year after I-131 therapy.

Results Among the 496 women, 87 (18 percent) had died or were lost to follow up. Among the remaining 409 women, 326 had normal menstrual cycles (Table). The women who had menstrual irregularities or transient amenorrhea (4 to 10 months) received more I-131, and those with transient amenorrhea were older. No woman had permanent amenorrhea.

Table. Menstrual Function and Pregnancies in 409 Women with Thyroid Cancer after Surgery and I-131 Therapy.

	Normal Menses	Menstrual Irregularities	Transient Amenorrhea
No. of women- (% of all women)	326 (80%)	49 (12%)	34 (8%)
Mean age at diagnosis-yr	31	28	36
Median I-131dose-mCi* (range)	80 (30-973)*	378 (30-810)	378 (230-1590)
No. wanting children (% of group)	253 (78%)	19 (39%)	4 (12%)
No. having pregnancies	253	18	4

*To convert to GBg, multiply by 0.037.

A total of 133 women (33 percent) reported that they did not want to have children and used contraception. Among the 276 women (67 percent) who wanted to have children, 275 had a total of 427 children.

Conclusion In women with thyroid cancer I-131 therapy may transiently impair ovarian function, but it has little long-term deleterious effect on fertility.

COMMENTARY

These are reassuring results, but it should be kept in mind that they were obtained retrospectively, many years after treatment in some women. Little is said about the outcome of the pregnancies, except that there were 14 spontaneous abortions (5 percent, an unusually low percentage), 4 premature births, and no fetal abnormalities. Also, whether the women who did have children had difficulty becoming pregnant or wanted more children is not stated, and therefore they may not have been normally fertile. The finding that relatively fewer women in the menstrual-irregularity and transient-amenorrhea groups said they wanted to have children may reflect their concern that the menstrual disorder might impair fertility or have harmful effects on a fetus, or that their long-term prognosis was poor.

These results complement those of a larger study of women with thyroid cancer that focused on the outcome of pregnancy (1). Among 923 women who had 2113 pregnancies, 1770 pregnancies (84 percent) had occurred before diagnosis of thyroid cancer, 85 (4 percent) after surgery alone, and 258 (12 percent) after surgery and I-131 therapy. The rate of spontaneous abortion was 11 percent in women who had pregnancies before diagnosis, 20 percent in women who became pregnant between surgery and I-131 therapy, and 20 percent in women who became pregnant after I-131 therapy (it was 40 percent in the 10 women who received 10 mCi [370 MBq] I-131 or more during the year preceding pregnancy). The incidence of stillbirth, premature delivery, and congenital anomalies was similar in the pregnancies that preceded and followed the diagnosis of thyroid cancer.

Women with thyroid cancer should be informed that fertility may occasionally be impaired, but that the outcome of pregnancy is not different from that in normal women unless the pregnancy occurs soon after I-131 therapy.

Robert. D. Utiger, M.D.

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Surgical resection of bone metastases may prolong survival in patients with thyroid carcinoma

Zettinig G, Fueger BJ, Passler C, Kaserer K, Pirich C, Dudczak R, Niederle B. Long-term follow-up of patients with bone metastases from differentiated thyroid carcinoma - surgery or conventional therapy? Clin Endocrinol 2002;56: 377-82.

SUMMARY

Background Some patients with differentiated thyroid carcinoma have bone metastases at the time of diagnosis or later in their course. This study evaluated the effect of surgical treatment of bone metastases on the course and outcome in patients with thyroid carcinoma.

Methods Between 1965 and 2001 710 patients with differentiated thyroid carcinoma were treated by thyroidectomy at the Vienna University Hospital. Among them, 497 patients (70 percent) had papillary carcinoma and 213 (30 percent) had follicular carcinoma.

Results Bone metastases were found in 41 of the 710 patients (6 percent) at the time of diagnosis of thyroid carcinoma or during follow-up. These 41 patients (24 women and 17 men; mean age, 60 years [range, 29 to 88]) included six of the 497 patients (1 percent) with papillary carcinoma and 35 of the 213 patients (16 percent) with follicular carcinoma. The primary tumor was <1 cm in diameter in 3 patients, 1 to 4 cm in 16 patients, >4 cm in 11 patients, and extended beyond the thyroid in 11 patients.

In 15 patients (36 percent) pain caused by a bone metastasis was the presenting symptom of thyroid carcinoma; seven patients had one bone metastasis and eight patients had multiple bone metastases. The bone metastases were detected within three months after diagnosis of thyroid carcinoma in 13 patients (32 percent), and 16 to 350 months after diagnosis in the other 13 patients (32 percent). At first detection, 28 patients (68 percent) had a single bone metastasis, 13 of whom later had other bone metastases, and 13 patients (32 percent) had multiple metastases. The first sites of metastasis were: femur, 15; thoracic spine, 10; lumbar spine, 10; pelvis, 9; sternum, 6; cervical spine, 5; and other sites, 20. Twenty-two of the 41 patients (54 percent) had only bone metastases, and 19 patients (46 percent) had metastases to other sites (lungs, 14 patients; liver, 1 patients; brain, 1 patients; adrenal, 1 patients; lung, brain, and liver, 1 patient).

All the patients were treated by thyroidectomy, and 32 (78 percent) received radioiodine (I-131) therapy, in doses ranging from 60 to 3000 mCi (2.2 to 111 GBq). In 21 patients (51 percent) the bone metastases were surgically resected; single metastases were resected in 15 patients, and two, three, and five metastases in two, three, and one patient, respectively. The metastases were treated by external-beam radiotherapy in 11 patients (27 percent), and chemotherapy in four patients (10 percent); four patients (10 percent) received no therapy for their bone metastases.

The 5- and 10-year survival rates in the 41 patients from the time of diagnosis of thyroid carcinoma were 69 percent and 39 percent, respectively. The 5- and 10-year survival rates from the time of first detection of bone metastases were 59 percent and 38 percent, respectively. The survival rate was statistically significantly higher in patients treated by total thyroidectomy, those treated with I-131, and those who did not have non-skeletal metastases. Among the patients with metastases only to bone, surgery was associated with improved survival. Tumor histology was not a determinant of survival.

Conclusion Patients with metastatic thyroid carcinoma who have only bone metastases may benefit from surgical resection of the metastases.

COMMENTARY

Bone metastases are uncommon in patients with papillary or follicular carcinoma, occurring in 5 to 10 percent of patients (1,2). Most of the patients are aged 50 years or older. The bone metastases may be present at the time of diagnosis, and indeed may be the initial manifestation of the thyroid carcinoma. About half of patients have multiple bone metastases, and similarly about half have non-bone metastases. And the metastases concentrate I-131 in only about half the patients. The most common sites of bone metastasis are the spine, pelvis, and femur. With respect to treatment, Zettinig et al. focused more on surgery than have other authors, and it seems clear that they think it has value, particularly in patients with a single bone metastasis and no non-bony metastases, a suggestion also made elsewhere (2).

Clinicians caring for patients with thyroid carcinoma need to be aware that patients can have bony metastases at the time of diagnosis or later. There is no one best method to detect these metastases. Nor are there clear indications for I-131 therapy, surgery, or radiation therapy, beyond saying that I-131 therapy is inappropriate if the metastases do not concentrate I-131, and surgery is appropriate if a metastasis is or is likely to be associated with a pathological fracture and stabilization of the bone is needed.

Robert D. Utiger, M.D.

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Questions?
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