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Patients with hyperthyroidism caused by Graves' disease may have serum antineutrophil cytoplasmic and antinuclear antibodies

Guma M, Salinas I, Reverter JL, Roca J, Valls-Roc M, Juan M, Olive A. Frequency of antineutrophil cytoplasmic antibody in Graves' disease patients treated with methimazole. J Clin Endocrinol Metab 2003;88:2141-6.

SUMMARY

Background High serum concentrations of antineutrophil cytoplasmic antibodies are associated with systemic vasculitis and glomerulonephritis, and high serum concentrations of antinuclear antibodies are associated with systemic lupus erythematosus and related disorders. Both types of antibodies have been found in patients with hyperthyroidism caused by Graves' disease, with the strongest association being between antineutrophil cytoplasmic antibodies and propylthiouracil therapy. In this study serum antineutrophil cytoplasmic and antinuclear antibodies were measured in patients with Graves' hyperthyroidism before and during methimazole therapy.

Methods The study subjects were 30 consecutive patients (25 women, 5 men; mean age, 36 years [range, 23 to 56]) with hyperthyroidism caused by Graves' disease. All the patients had overt hyperthyroidism, a diffuse goiter, and a high serum concentration of thyrotropin (TSH)-receptor antibodies (measured by receptor assay). They were treated with methimazole for 11 to 17 months.

Serum antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), and antithyroid antibodies were measured at base line and periodically during and at the end of treatment. Serum ANCA were measured by immunofluorescence; diffuse granular cytoplasmic staining defined the presence of cytoplasmic (c-) ANCA, staining around the cell nuclei the presence of perinuclear (p-) ANCA, and diffuse nongranular cytoplasmic staining the presence of atypical (x-) ANCA. Enzyme-linked immunoassays were used to detect individual neutrophil antigens (see below). Serum ANA were measured by immunofluorescence using human epithelioma cells; the staining patterns were reported as homogeneous or speckled. Serum anti-double-stranded DNA (dsDNA) antibodies were measured by immunofluoresence using *Crithidia luciliae* as antigen.

Results At base line, ANCA were detected in the serum of 15 patients (50 percent); 12 patients (40 percent) had p-ANCA, 1 patient (3 percent) had c-ANCA, and 2 patients (7 percent) had x-ANCA. Fifteen patients (50 percent) had antibodies against one or more individual neutrophil antigens (proteinase 3, myeloperoxidase, bactericidal/permeability-increasing protein, cathepsin, lactoferrin, and lysozyme). Overall, 20 patients (67 percent) had a positive test for ANCA or one or more neutrophil antigens. There were no correlations between ANCA and serum antithyroid peroxidase, antithyroglobulin, or TSH-receptor antibodies. After treatment for three to six months, the ANCA disappeared in 6 patients and appeared in 1 patient. Twenty-one patients were studied at the end of treatment; among the 12 patients who had ANCA at base line the antibodies disappeared in 8 and persisted in 4.

Before treatment, ANA were detected in the serum of 22 patients (73 percent) and dsDNA antibodies were detected in the serum of 3 patients (10 percent). The ANA titers ranged from 1/80 to 1/1280, with a speckled pattern in 11 patients (37 percent) and a homogeneous pattern in 11 patients (37 percent). There was no change in ANA titers during treatment.

No patient had any manifestations of vasculitis at any time.

Conclusion Some patients with Graves' hyperthyroidism have ANCA, which tend to disappear during antithyroid drug treatment. ANA are detected more commonly, and do not disappear during treatment.

COMMENTARY

ANCA (and ANA) have been detected before treatment in other patients with Graves' hyperthyroidism, but considerably less often than in this study (1,2). Among patients receiving an antithyroid drug in whom ANCA were detected, nearly all were taking propylthiouracil, although very few had vasculitis. The findings in this study provide further evidence that methimazole does not induce the production of ANCA.

Setting aside the relationship between propylthiouracil therapy and ANCA, might ANCA (and ANA) have a role in the pathogenesis of Graves' disease? That seems unlikely. Given the antigens with which these antibodies react, it is difficult to construct a model in which either ANCA or ANA could contribute either to the production or the action of the TSH-receptor antibodies that are the cause of hyperthyroidism in patients with Graves' disease. More likely, the production of ANCA and ANA is an epiphenomenon, caused by the same loss of tolerance to self-antigens that results in production of TSH-receptor antibodies and hyperthyroidism.

Robert D. Utiger, M.D.

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Certain personality traits and many daily hassles are associated with recurrent hyperthyroidism in Graves' disease

Fukao A, Takamatsu J, Murakami Y, Sakane S, Miyauchi A, Kuma K, Hayashi S, Hanafusa T. The relationship of psychological factors to the prognosis of hyperthyroidism in antithyroid drug-treated patients with Graves' disease. Clin Endocrinol 2003;58:550-5.

SUMMARY

Background Whether psychological factors are important in the initiation of Graves' disease and the resulting hyperthyroidism has been debated for many years. This study was done to determine if psychological factors are important in determining remission after the cessation of antithyroid drug therapy in these patients.

Methods The study subjects were 69 patients with Graves' hyperthyroidism who had been treated with an antithyroid drug for two to five years and were euthyroid. The number of patients eligible for the study is not given; of those invited to participate 72 agreed, and 69 completed the study questionnaires and had measurements of thyroid volume and serum thyrotropin (TSH), free thyroxine (T_4), and TSH-receptor antibody activity (radioreceptor assay). The antithyroid drug was then discontinued, and the patients were followed for one year. Those who had a high serum free T_4 and a low serum TSH concentration during follow-up were considered to have relapsed, and those in whom the values remained normal were considered to be in remission. The same questionnaires were completed by 32 normal subjects of similar age, sex, and socioeconomic status.

Three questionnaires were used. One was the Minnesota Multiphasic Personality Inventory (Japanese version), which has 10 parts (383 questions) covering 10 personality traits such as hypochondriasis, mental fatigue, and depression, with higher scores indicating more features of the relevant trait. The second was a general stress inventory, with 67 questions about the patient's personal, family, occupational, and social life, such as pregnancy, death of spouse, and retirement, in the previous year. These items were scored on a scale of 0 to 100, with higher scores indicating more stress. The third was an inventory of stress in daily life, with 71 questions about daily hassles, such as feeling short of time and often annoyed by others, and daily uplifts, such as work satisfaction and peaceful home life, in the previous year. These items were scored on a three-point scale according to their impact.

Results Forty-one of the 69 patients (59 percent) had recurrent hyperthyroidism (relapse group) and 28 patients (41 percent) remained euthyroid (remission group) during the year after cessation of antithyroid drug therapy. The mean age and proportion of women and men were similar in the two groups. At the time of cessation of therapy, their mean serum free T_4 concentrations were the same (1.3 ng/dl [16.8 pmol/L]), whereas the mean serum TSH concentration was lower (0.8 vs. 1.9 mU/L) and thyroid volume (44 vs. 23 ml) and serum TSH-receptor antibody activity (25 vs. 3 percent) were higher in the relapse group ($P<0.05$, for the three comparisons).

The patients in the relapse group had higher scores for hypochondriasis, depression, paranoia, and mental fatigue than the remission group ($P<0.05$). The frequency and total scores for major stressful life events, daily stressful events, and daily uplifts were not different in the two groups, but the score for daily hassles was higher in the relapse group (42 vs. 35 [of 80], $P<0.05$). The results in the normal subjects were similar to those in the remission group.

Conclusion Among patients with Graves' hyperthyroidism being treated with an antithyroid drug, those who have certain personality traits and have more daily hassles are more likely to have recurrent hyperthyroidism after the cessation of therapy than those who remain in remission.

COMMENTARY

If psychological factors can initiate Graves' disease, then it is reasonable to assume that these factors might also perpetuate it. The evidence for the former is controversial (1), and that provided in this paper does not provide much support for the latter, the only differences among the many comparisons being slightly higher scores for daily hassles and some personality traits in the patients who had recurrent hyperthyroidism. It seems unlikely that the differences would have been greater had the duration of treatment varied less, or had the patients been euthyroid for a similar length of time before the questionnaires were administered (this is not stated, but probably varied substantially given the varying overall duration of treatment).

Most previous studies of the possible relationship between psychological factors and Graves' disease focused on life stresses, not personality traits. The latter surely are important in determining how life stresses might affect the person's behavior, and so might be important in determining how the former might initiate Graves' disease, if there is indeed a cause-and-effect relationship.

The personality inventory used in this study might not be the best way to determine these traits, but the approach may be worth pursuing.

Robert D. Utiger, M.D.

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Prednisone is more effective than iopanoic acid in hyperthyroidism caused by amiodarone-induced thyroiditis

Bogazzi F, Bartalena L, Cosci C, Brogoni S, Dell'Unto E, Grasso L, Aghini-Lombardi F, Rossi G, Pinchera A, Braverman LE, Martino E. Treatment of type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. J Clin Endocrinol Metab 2003;88:1999-2002.

SUMMARY

Background Amiodarone causes two types of hyperthyroidism, iodine-associated hyperthyroidism (type I) and thyroiditis-associated hyperthyroidism (type II). Patients with the latter have been treated with antithyroid drugs, glucocorticoids, oral cholecystographic agents, and thyroidectomy, with varying efficacy. This study was done to compare the efficacy of prednisone and iopanoic acid (an oral cholecystographic agent) in patients with hyperthyroidism caused by amiodarone-induced thyroiditis.

Methods The study subjects were 12 patients taking amiodarone who had thyroiditis-associated hyperthyroidism, as defined by biochemical hyperthyroidism; absence of thyroid enlargement, as determined by ultrasonography; thyroid hypovascularity, as determined by color-flow ultrasonography; low thyroid radioiodine uptake; and normal serum concentrations of several thyroid antibodies. They had taken amiodarone for an average of approximately 30 months, and it was stopped on study entry.

The patients were randomly assigned to receive prednisone or iopanoic acid. The initial dose of prednisone was 30 mg daily orally; after which it was gradually tapered over a three-month period and then stopped. Iopanoic acid was given in a dose of 500 mg orally twice daily until the patient had normal serum free thyroxine (T_4) and free triiodothyronine (T_3) concentrations. Serum free T_4, free T_3, and thyrotropin (TSH) were measured at base line, weekly for one month, and monthly thereafter.

Results There were 4 men and 2 women in the prednisone group (mean age, 65 years) and 5 men and 1 woman in the iopanoic acid group (mean age, 64 years). Their base-line serum free T_4 and free T_3 concentrations were similar, and all had undetectable serum TSH concentrations (<0.005 mU/L).

After the initiation of therapy, the mean serum free T_3 concentration decreased to within the normal range in seven days and remained normal thereafter in both groups. The mean serum free T_4 concentration decreased promptly in the prednisone group, reaching the normal range by 14 days, whereas it changed little in the iopanoic acid group until 180 days. The mean (±SD) serum TSH concentration was normal in 40±34 days in the prednisone group and 84±43 days in the iopanoic acid group.

Symptoms of hyperthyroidism (types and severity not stated) improved as serum free T_3 concentrations declined. All the patients in the prednisone group had normal serum free T_4 and free T_3 concentrations by 90 days (mean, 43±34 days), as compared with 360 days (mean, 221±111, P<0.01) in the iopanoic acid group. Two patients in the iopanoic acid group, but none in the prednisone group, had recurrent hyperthyroidism after therapy was discontinued.

Conclusion In patients treated with hyperthyroidism caused by amiodarone-induced thyroiditis, prednisone is more effective treatment than is iopanoic acid.

COMMENTARY

There is no denying that amiodarone causes hyperthyroidism, as defined by changes in serum thyroid hormone and TSH concentrations. What is less clear is its clinical importance. Few of the studies of patients who had hyperthyroidism while taking amiodarone, including this one, include any detailed assessment of clinical status at base line or of changes in clinical status during therapy. The authors of this study do say that the patients had some symptoms of cardiac dysfunction that improved as their serum free T_3 concentrations fell, but what those symptoms were and whether other therapy, for example a beta-adrenergic antagonist drug, was given at the same time is not stated.

The superiority of prednisone as compared with iopanoic acid in restoring normal thyroid function in this study is clear, even though it may be no more effective in ameliorating symptoms acutely. Therefore, iopanoic acid (and its analogs) should be relegated to footnote status. How does prednisone compare with an antithyroid drug? While the rationale for antithyroid drug therapy in patients with thyroiditis is quite uncertain, it has been thought to be effective, although its action is so slow that the benefit could be due to spontaneous remission (1). In a 40-day study in which an antithyroid drug was compared with prednisone and an antithyroid drug, serum T_4 concentrations changed little in the former group and declined by approximately 30 percent in the latter group (2). If treatment is needed, prednisone seems most appropriate, but it is doubtful that all patients with amiodarone-induced thyroiditis and hyperthyroidism need treatment.

Robert D. Utiger, M.D.

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Fixed doses of I-131 are as effective as adjusted doses for treatment of hyperthyroidism caused by Graves' disease

Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab 2003;88:978-83.

SUMMARY

Background Iodine-131 (I-131) is a standard treatment for hyperthyroidism caused by Graves' disease. There is no widely accepted method for estimating dosage, and the methods used for this purpose have only occasionally been directly compared. In this study four methods of dose estimation were evaluated.

Methods The study subjects were 88 patients (66 women, 22 men; mean age, 41 years) with hyperthyroidism caused by Graves' disease. They represented 33 percent of the 264 potentially eligible patients referred for a first dose of I-131 during the study period; the two groups were similar except that the study subjects were younger and had higher serum thyroxine (T_4) concentrations before any therapy. The diagnosis of Graves' hyperthyroidism was based on the presence of clinical and biochemical hyperthyroidism, diffuse goiter, and high thyroid I-131 uptake values. Most patients (percentage not given) had received an antithyroid drug for 9±16 (mean ±SD) months before being referred for I-131 therapy; the drug was stopped five days before measurement of I-131 uptake.

After measurement of I-131 uptake, and stratification according to 4-hour uptake (<50 or ≥50 percent) and thyroid size (<40, 40 to 80, >80 g, estimated by palpation by a single examiner at the time of I-131 therapy), the patients were randomly assigned to receive a therapeutic dose of I-131 calculated by one of four methods; low fixed dose, 6.4 mCi (235 MBq); high fixed dose, 9.4 mCi (350 MBq); low adjusted dose, 80 μCi (2.96 MBq)/g; and high adjusted dose, 120 μCi (4.44 MBq)/g (the adjustment was for fractional 24-hour I-131 uptake as well as weight). The patients were evaluated by the referring physician six weeks after treatment and periodically thereafter; neither the patient nor the physician knew of the treatment-group assignment. The primary outcomes were persistent or recurrent hyperthyroidism; hypothyroidism, confirmed on two occasions four weeks apart and treated with T_4; and normal thyroid function at the end of the follow-up period.

Results The characteristics of the patients in the four groups at the time of diagnosis of hyperthyroidism and of I-131 treatment were similar (Table). During a mean follow-up period of 80 months (range, 10 to 111), 21 patients (24 percent) had persistent or recurrent hyperthyroidism, 61 (69 percent) had hypothyroidism, and only 6 (7 percent) were euthyroid. There were no differences in outcome in the four treatment groups (Table).

Table. Characteristics of Patients with Graves' Hyperthyroidism Treated with I-131 and Outcomes of Treatment.

	Low Fixed Dose (n=22)	High Fixed Dose (n=23)	Low Adjusted Dose (n=22)	High Adjusted Dose (n=21)
Women/men	15/7	20/3	17/5	14/7
Age (yr)	39±12	44±15	42±14	38±13
Serum T_4 (μg/dl)	17.3±4.2	15.8±6.8	16.5±7.8	18.7±6.7
Thyroid volume (g)	74±52	67±46	62±35	58±30
4-Hour I-131 uptake (%)	51±20	50±25	51±24	50±20
24-Hour I-131 uptake (%)	57±14	59±18	59±18	57±15
I-131 dose (mCi)	6.4±0.2	9.5±0.3	8.5±4.4	12.3±6.0
Outcome (%)				
Hyperthyroidism	6 (27)	6 (26)	4 (18)	5 (24)
Hypothyroidism	16 (73)	15 (65)	18 (82)	12 (57)
Euthyroid	0 (0)	2 (9)	0 (0)	4 (19)

Values are means (±SD). To convert serum T_4 values to nmol/L, multiply by 12.9; and to convert mCi to MBq, multiply by 37.

The mean doses of I-131 administered to the patients in the three outcome groups were similar. The times to recurrent or persistent hyperthyroidism or hypothyroidism were also similar; in most patients the outcome was reached 4 to 6 months after treatment.

Conclusion Fixed doses of I-131 are as effective as doses adjusted according to thyroid size and I-131 uptake for treatment of hyperthyroidism caused by Graves' disease.

COMMENTARY

The results reported by Leslie et al. are interesting in several respects. The effects of an almost two fold range of doses were virtually identical, it didn't matter how the dose was calculated, and despite the varying doses the effects were evident within a relatively short time in all four groups. A dose-dependent effect of I-131 could have been missed if some of the patients in the higher-dose groups who had persistent or recurrent hyperthyroidism (not distinguished in the paper) had become euthyroid or hypothyroid if followed longer before being given an additional dose of I-131, but this seems unlikely.

Patients are treated with I-131 to ameliorate hyperthyroidism, and it is a disservice not to give enough I-131 to achieve this result. This may mean that every patient should be given a dose of 20 mCi (740 MBq). So be it. The cost of the additional I-131 is small, and the costs of inadequate therapy, both medical and economic, may be substantial. The case for doing it right the first time is compelling.

Robert D. Utiger, M.D.

The risk of neutropenia is higher for antithyroid drugs than many other classes of drugs

Van Staa TP, Boulton F, Cooper C, Hagenbeek A, Inskip H, Leufkens HG. Neutropenia and agranulocytosis in England and Wales: incidence and risk factors. Am J Hematol 2003;72:248-54.

SUMMARY

Background Many drugs, including the three most widely used antithyroid drugs—carbimazole, methimazole, and propylthiouracil—can cause idiosyncratic neutropenia or agranulocytosis in occasional patients. This study was undertaken to estimate the prevalence and outcome of neutropenia and agranulocytosis in England and Wales.

Methods The information for the study was obtained from the General Practice Research Database, which contains the medical records (including clinical events, prescription records, and hospital admissions) of patients cared for by general practitioners who serve approximately 6 percent of the population in England and Wales. The database was searched for the years 1988 to 1999 for patients with the diagnostic code for neutropenia (≤500 granulocytes/mm^3) or agranulocytosis in their records. Patients with aplastic anemia, sideroblastic anemia, and other blood dyscrasias, cancer, and systemic lupus erythematosus were excluded, as were patients who had received chemotherapy and immunosuppressive drugs. Drug exposure was determined by reviewing all prescription information before the date of diagnosis of neutropenia or agranulocytosis. Each case was matched to three control subjects of the same age, sex, and practice (excluding patients with the disorders listed above).

Results There were 3224 patients with neutropenia, of whom 50 (2 percent) had agranulocytosis; the estimated incidence rates were 120 and 7 cases/1 million people/year, respectively. Among 21 classes of drugs, the risk of neutropenia and agranulocytosis was highest for antithyroid drugs, aminosalicylates, disease-modifying antirheumatic drugs, and antiepileptic drugs (Table). With respect to antithyroid drugs, a specific drug, carbimazole, is mentioned in only one context (see following text).

Table. Risk of Neutropenia and Agranulocytosis.

	Neutropenia			Agranulocytosis		
	Cases (n=3224)	Controls (n=9321)	Odds Ratio (95%CI)	Cases (n=50)	Controls (n=144)	Odds Ratio (95%CI)
Antithyroid drugs	44	4	35 (12-100)	7	0	21 (3-∞)
Antirheumatic drugs*	41	8	10 (4-21)	2	0	6 (1-∞)
Aminosalicylates	98	30	8 (5-12)	5	2	9 (1-401)
Antiepileptic drugs	128	90	4 (3-5)	2	1	6 (1-276)
Antibacterial drugs	603	830	3 (2-3)	14	12	3 (1-8)
Non-opioid analgesic drugs	475	700	2 (1-2)	13	17	2 (1-5)

CI denotes confidence interval.
*Gold salts, penicillamine, hydroxychloroquine.

Among the patients with neutropenia, 77 (2 percent) died within one year, as compared 69 (1 percent) of the controls (adjusted relative risk 2; 95 percent confidence interval, 1 to 3). The major causes of death were cancer and cardiovascular disease. Five patients with neutropenia died of an infection (drug not stated), as compared with one control.

Among the 44 patients treated with an antithyroid drug who had neutropenia, 6 had received one prescription (vs. 1 of the controls), 16 patients had received 2 or 3 prescriptions (vs. 1 of the controls), and 22 patients had received 4 or more prescriptions (vs. 2 of the controls). With respect to drug dose, the risk of neutropenia in patients taking carbimazole was dose dependent. Fifteen patients were taking 5 to 15 mg daily (vs. 2 controls), and 24 patients were taking ≥20 mg daily (vs. 2 controls).

Conclusion Among many classes of drugs, the risk of neutropenia and agranulocytosis was highest in patients treated with an antithyroid drug.

COMMENTARY

This odds ratio for neutropenia is similar to that found in other studies. For example, from 1982 to 1991 5 patients taking an unnamed antithyroid drug were hospitalized for neutropenia in the Canadian province of Saskatchewan (vs. 1 of 3462 control subjects; odds ratio 874; 95 percent confidence interval, 92 to ∞) (1). From 1987 to 1990 15 patients taking methimazole and 2 patients taking carbimazole were hospitalized for neutropenia in the Netherlands. As compared with a cohort of 752 patients provided with these drugs at the same time, the relative risk for neutropenia was 115 (95 percent confidence interval, 60 to 219). There are no comparable case data for propylthiouracil. In the largest observational study, from Japan, the incidence of neutropenia among methimazole-treated patients was 0.31 percent (41 of 13,208 patients), and it was 0.55 percent among propylthiouracil-treated patients (12 of 2190 patients).

These results serve as a reminder that antithyroid drugs have serious side effects. Nonetheless, the risk of neutropenia is very low, it is apparently dose-related (at least for carbimazole–methimazole), and it is rarely fatal.

Robert D. Utiger, M.D.

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MRNAs for the TSH receptor and proinflammatory cytokines are present in orbital tissue in active Graves' ophthalmopathy

Wakelkamp IM, Bakker O, Baldeschi L, Wiersinga WM, Prummel MF. TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. Clin Endocrinol 2003;58:280-7.

SUMMARY

Background Graves' ophthalmopathy is characterized by inflammation of orbital fibroadipose tissue and muscle, but the underlying causes(s) of the inflammatory process is not known. Orbital tissue contains thyrotropin (TSH) receptors and cytokines, both of which, if activated, might lead to orbital inflammation. In this study the levels of messenger RNA (mRNA) for TSH receptors and several cytokines were measured in orbital tissue obtained from patients with active and inactive Graves' ophthalmopathy.

Methods Orbital fibroadipose tissue was obtained at the time of orbital decompression surgery from 17 patients with Graves' ophthalmopathy. Six of the patients (all women; mean [±SD] age, 50±12 years) had active ophthalmopathy, as defined by a clinical scoring system (mean score, 7 of a possible 10 points), for an average of six months. They underwent decompression to relieve optic neuropathy (5 patients) or fixation of the orbits (1 patient). Eleven patients (9 women, 2 men; mean age 45±13 years) had chronic inactive ophthalmopathy (mean activity score, 2). The mean duration of ophthalmopathy in this group was 36 months, and none had any change in the preceding six months. They underwent decompression for "rehabilitative" reasons (presumably for relief of marked exophthalmos). All patients were euthyroid at the time of surgery.

RNA was extracted from the orbital fibroadipose tissue and reverse-transcribed to form cDNA. The cDNA was amplified quantitatively by the polymerase chain reaction using primers for the TSH receptor, interferon-γ, tumor necrosis factor-α, and multiple interleukins (IL). The results were quantitated by comparison with serial dilutions of the products of amplification of cDNA prepared from TSH-receptor and cytokine mRNA extracted from thyroid tissue, peripheral blood mononuclear cells, or T lymphocytes.

Results TSH-receptor mRNA was detected in the tissue from 5 of the 6 patients (83 percent) with active ophthalmopathy, as compared with 2 of the 11 patients (18 percent) with inactive ophthalmopathy. The relative content of TSH-receptor mRNA was also considerably higher in the tissue from the patients with active ophthalmopathy. With respect to the cytokines, the mRNAs for the cytokines considered to promote cellular inflammation (Th1-directed cytokines), such as IL-1β, IL-2, IL-6, IL-8, and IL-10, were detected in a higher proportion of or in greater amounts in the tissues from patients with active ophthalmopathy. In contrast, there were no differences in the mRNAs for cytokines linked more with antibody production and action (Th2-directed cytokines), such as IL-2R, IL-3, IL-4, IL-5, and IL-18. The mRNAs for interferon-γ and tumor necrosis-α mRNA (Th1) were not detected more often or in greater amounts in the active-ophthalmopathy group.

Conclusion mRNAs for the TSH receptor and inflammatory cytokines can be detected more often and in greater amounts in orbital fibroadispose tissue from patients with active Graves' ophthalmopathy than those with inactive ophthalmopathy.

COMMENTARY

Graves' ophthalmopathy is characterized by inflammation and therefore enlargement of orbital fibroadipose tissue and extraocular muscle. The muscle enlargement, as detected by imaging, is the more characteristic clinical feature of the disorder. However, most of the mechanistic studies of the disorder have focused on changes in orbital fibroadipose tissue, because it is much easier to obtain pieces of this tissue.

These studies, like the present one, have revealed mRNA for the TSH receptor and also various cytokines in orbital tissue (1,2). For the most part these mRNAs, particularly TSH-receptor mRNA, were found in greater abundance, and sometimes only, in tissue obtained from patients with Graves' ophthalmopathy. The presence of mRNA in tissue is routinely referred to as expression, but the particular protein may not be synthesized in important quantities, or it may not be processed properly after synthesis or reach its normal location, which in the case of the TSH receptor is the cell membrane. So, the detection of mRNA for a protein does not automatically mean that the protein is functionally active, much less that it is involved in disease.

That note of caution aside, the notion that Graves' ophthalmopathy might in some way result from activation of TSH receptors in orbital tissue is appealing, and parsimonious. If antibodies activate TSH receptors on thyroid tissue, causing hyperthyroidism, then why shouldn't the same antibodies activate TSH receptors in orbital tissue, somehow causing orbital inflammation, mediated through a host of cytokines? This seems plausible, and it leads to questions such as, are the receptors present in orbital tissue in everyone, and if so, what do they do? And if they are present, why don't all patients with Graves' disease have ophthalmopathy, and why aren't the receptors activated by the high serum TSH concentrations of patients with hypothyroidism?

Robert D. Utiger, M.D.

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Serum C-reactive protein and homocysteine concentrations are raised in women with hypothyroidism

Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, Muller B. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis 2003;166:379-86.

SUMMARY

Background High serum C-reactive protein and homocysteine concentrations are independent risk factors for arteriosclerotic cardiovascular disease. Overt and subclinical hypothyroidism may also be a risk factor for the disease. In this study, serum C-reactive protein and homocysteine were measured in patients with overt hypothyroidism and before and during thyroxine (T_4) therapy in patients with subclinical hypothyroidism.

Methods The study subjects were 61 women (mean [±SD] age, 56±12 years) with overt hypothyroidism, 63 women (mean age, 58±10 years) with subclinical hypothyroidism, and 40 normal women (mean age, 54±9 years). Most of the women with hypothyroidism had chronic autoimmune thyroiditis. The 63 women with subclinical hypothyroidism were randomly assigned to receive T_4 or placebo for 48 weeks. Serum thyrotropin (TSH), free T_4, C-reactive protein, homocysteine, creatinine, vitamin B_{12}, and folic acid were measured once in the women with overt hypothyroidism and the normal women and before and after T_4 therapy in the women with subclinical hypothyroidism.

Results Serum C-reactive protein concentrations were higher in the women with overt hypothyroidism and those with subclinical hypothyroidism than in the normal women (Table 1). For all women, serum C-reactive protein concentrations were positively correlated with age and body-mass index, but not with serum TSH or free T_4 concentrations. As compared with the normal women, serum homocysteine concentrations were higher in the women with overt hypothyroidism, but not in the women with subclinical hypothyroidism. Serum homocysteine concentrations were positively correlated with serum TSH and creatinine concentrations and age, and negatively correlated with serum free T_4, vitamin B_{12}, and folic acid concentrations.

Table 1. Mean (±SD) Serum TSH, Free T_4, C-Reactive Protein and Homocysteine Concentrations in Women with Overt and Subclinical Hypothyroidism and Normal Women.

	Overt Hypothyroidism (n=61)	Subclinical Hypothyroidism (n=63)	Normal (n=40)	P Value
Serum TSH (mU/L)	43±32	11±6	1.5±0.6	<0.01
Serum free T_4 (ng/dl)	0.4±0.2	0.9±0.1	1.2±0.2	<0.01
Serum C-reactive protein (mg/L)	2.8±2.4	2.6±2.3	1.8±1.9	0.03
Serum homocysteine (μmol/L)	14.4±9.1	11.0±2.7	11.3±2.8	<0.01

To convert serum free T_4 values to pmol/L, multiply by 12.9.

The serum C-reactive protein and homocysteine concentrations in the women with subclinical hypothyroidism did not change after T_4 therapy (mean dose, 84 μg/day) for 48 weeks, whereas their serum TSH concentrations declined (P<0.001) (Table 2). There were no changes in any values in the placebo group.

Table 2. Mean (±SD) Serum TSH, C-Reactive Protein, and Homocysteine Concentrations in Women with Subclinical Hypothyroidism before and after T_4 Therapy for 48 Weeks.

	T_4 Therapy (n=31)		Placebo (n=32)	
	Before	After	Before	After
Serum TSH (mU/L)	11.4±6.6	3.1±1.7	10.1±4.8	9.9±3.7
Serum C-reactive protein (mg/L)	2.9±2.6	2.8±2.6	2.3±2.0	2.9±2.7
Serum homocysteine (μmol/L)	10.3±2.5	11.1±3.4	11.7±2.7	12.0±3.6

Conclusion Serum C-reactive protein and homocysteine concentrations are slightly higher in women with overt hypothyroidism than in normal women. In contrast, in women with subclinical hypothyroidism only serum C-reactive protein concentrations are high, and T_4 therapy does not lower them.

COMMENTARY

Whether hypothyroidism is a risk factor for arteriosclerosis and cardiovascular disease has been debated; suffice it to say that the evidence is inconclusive. That evidence could of course be strengthened only very indirectly by this study of the postulated risk factors C-reactive protein and homocysteine. The serum C-reactive protein concentrations were slightly higher in both groups of women with hypothyroidism than in the normal women, and they did not change during prolonged T_4 therapy in the women with subclinical hypothyroidism. Perhaps the higher values in the women with both overt and subclinical hypothyroidism were caused by the low-grade inflammation of chronic autoimmune thyroiditis rather than hypothyroidism.

Serum homocysteine concentrations were higher in the women with overt hypothyroidism than the other women, but the increases were correlated as well as or better with other factors (age, renal function, vitamin B_{12}, and folate status) than with thyroid function. High serum homocysteine concentrations have been found in other patients with overt hypothyroidism, and the concentrations fell with T_4 therapy (1), but not patients with subclinical hypothyroidism (2).

Robert D. Utiger, M.D.

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Thyroxine therapy may increase fecundity in infertile women with mild hypothyroidism

Raber W, Nowotny P, Vytiska-Binstorfer E, Vierhapper H. Thyroxine treatment modified in infertile women according to thyroxine-releasing hormone testing: 5 year follow-up of 283 women referred after exclusion of absolute causes of infertility. Hum Reprod 2003;18:707-14.

SUMMARY

Background Women with overt hypothyroidism may be infertile, but the extent to which women with infertility have hypothyroidism and the effect of thyroxine (T_4) therapy on their infertility are uncertain. In this study thyroid function was assessed in infertile women, and then the effect of T_4 therapy on infertility was determined in the women who had thyroid dysfunction.

Methods The study subjects were women with infertility who were evaluated for thyroid dysfunction as part of a standard work-up for their infertility. All had been unable to conceive despite unprotected intercourse for one year, although some had pregnancies earlier. Women with overt hypothyroidism or bilateral tubal obstruction and those whose partners had azoopsermia were excluded.

Thyroid status was assessed by measurements of serum T_4, triiodothyronine (T_3), thyroxine-binding globulin (TBG), antithyroid peroxidase and antithyroglobulin antibodies, and thyrotropin (TSH); the latter was measured basally and 20 minutes after administration of 400 μg of thyrotropin-releasing hormone (TRH). All the women had normal serum T_4, T_3, and TBG concentrations. The women were subdivided as follows: subclinical hypothyroidism, serum TSH concentration >4 mU/L; exaggerated TRH response, basal serum TSH concentration ≤4 mU/L and serum TSH response to TRH >25 mU/L; euthyroid, basal serum TSH concentration ≤4 mU/L and normal serum TSH response to TRH; and no TRH test, basal serum TSH concentration ≤4 mU/L and TRH test not done. Approximately 70 percent of the women with subclinical hypothyroidism had high serum antithyroid antibody concentrations, as compared with approximately 25 percent in the other groups. All the women were seen at three-month intervals, and more often if they were pregnant. The women in the subclinical hypothyroidism and exaggerated TRH response groups were treated with T_4. Twelve percent of the women dropped out of the study after initial evaluation.

Results The mean (±SD) age of the 217 women who were followed was 32±7 years. They had been infertile for approximately 2.5 years. During a mean follow-up period of 20±14 months, 82 of the women (38 percent) became pregnant. The pregnancy, spontaneous abortion, and delivery rates were similar in the four groups (Table). All the abortions occurred during the first trimester, and were not related to the presence of autoimmune thyroiditis.

Table. Pregnancies and Outcomes of Pregnancy in Infertile Women as a Function of Thyroid Status at Base Line.

	Pregnancy	Abortion	Delivery*
Subclinical hypothyroidism (n=75)	24 (32%)	15 (20%)	15 (22%)
Exaggerated TSH response (n=56)	26 (46%)	10 (18%)	15 (30%)
Normal (n=51)	19 (37%)	1 (2%)	14 (28%)
No TRH test (n=35)	13 (37%)	0 (0%)	8 (24%)

*Some women in each group (6 to 12 percent) had not delivered.

The pregnancy rate was higher in younger women and in those in whom serum TSH concentrations were <2.5 mU/L during follow-up. In contrast, duration of infertility, duration of follow-up, or presence of autoimmune thyroiditis were not determinants of the pregnancy rate.

Conclusion Women who have minor degrees of thyroid hypofunction and are treated with T_4 have pregnancy, abortion, and delivery rates similar to women with normal thyroid function.

COMMENTARY

There are some curious aspects to this study. One, little is said about the women's infertility except for the absence of bilateral tubal obstruction and of azoospermia in the partner. Presumably women with endometriosis, anovulatory cycles, or other disorders associated with infertility were not referred to the authors' clinic for thyroid evaluation. Two, even among the women who were enrolled in the study, it seems unlikely that other treatments, for example, ovulation induction with clomiphene, were not offered. Three, the only thyroid abnormality in a substantial proportion of the women was an exaggerated serum TSH response to TRH. This is not a highly reproducible test, and the basal serum TSH and T_4 concentrations and the frequency of autoimmune thyroiditis in these women were similar to those in the women with normal serum TSH responses to TRH.

This study does not demonstrate that T_4 therapy increases fertility in women with mild thyroid hypofunction, because all the women in the two thyroid dysfunction groups were treated. On the other hand, the therapy had no deleterious effect. The latter would not be expected, given the care taken to avoid overtreatment (the average T_4 doses ranged from 45 to 84 μg daily in the different groups). In another study of screening for hypothyroidism in infertile women, 16 of 704 women (2 percent) had subclinical hypothyroidism; among them only the 11 women who also had ovulatory dysfunction had pregnancies when treated with T_4 (1).

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Thyroid hormone therapy is not a risk factor for hip fracture in older women

Van Den Eeden SK, Barzilay JI, Ettinger B, Minkoff J. Thyroid hormone use and the risk of hip fracture in women ≥65 years: a case-control study. J Womens Health 2003;12:27-31.

SUMMARY

Background Thyroid hormone therapy has been associated with osteoporosis, but in several studies was not associated with fracture. This study, using case–control methodology, was done to determine the relationship between thyroid hormone therapy and hip fracture.

Methods The study subjects were women aged ≥65 years who were members of a large group health plan in Northern California. The cases were 501 women who were randomly selected from among 1047 women who were hospitalized because of a hip fracture between 1971 and 1975. The controls were 533 women matched to the cases for age (±1 year) and year of entry into the health plan who had not had a hip fracture before the date of fracture of the cases with which they were matched.

The medical records of these women were reviewed by an analyst who did not know the women's case or control status. Data were collected on history of thyroid disease; therapy with thyroid hormone, estrogen, glucocorticoids, and hydrochlorothiazide; menopausal status; visual difficulties; and number of falls requiring emergency department care.

Results The characteristics of the women in the hip-fracture and control groups were similar, in terms of age, racial/ethnic origin, menopausal status, and tobacco and alcohol use. Approximately 25 percent were aged 65 to 69 years, 50 percent were aged 70 to 79 years, and 25 percent were aged 80 years or older; 95 percent were white.

The frequency of a history of thyroid disorders and therapy with thyroid hormone was similar in the two groups (Table). No woman in either group had thyroid carcinoma. There was no increase in risk of fracture with higher doses of thyroid hormone.

Table. Thyroid Disorders and Thyroid Hormone Therapy in Women with Hip Fracture and Control Women.

	Hip-Fracture Group	Control Group	Odds Ratio (95% CI)
Hypothyroidism	36 (7%)	31 (6%)	1.3 (0.8-2.2)
Hyperthyroidism	13 (3%)	9 (2%)	1.6 (0.7-3.8)
Thyroid hormone therapy			
No	436 (87%)	466 (87%)	1.0
Yes	65 (13%)	67 (13%)	1.1 (0.8-1.6)
≤4 years	31 (6%)	34 (6%)	1.0 (0.6-1.7)
≥5 years	34 (7%)	33 (6%)	1.2 (0.7-1.9)
Time since last dose*			
≤5 years	42 (8%)	46 (9%)	1.0 (0.7-1.6)
≥6 years	19 (4%)	20 (4%)	1.0 (0.5-1.9)

CI denotes confidence interval
*Data missing for some women.

Among the other variables examined, only a history of falls was more common in the hip-fracture group (35 vs. 23 percent; odds ratio 1.8; 95 percent confidence interval, 1.4 to 2.4). Adjustment for this or the other variables had little effect on the odds ratios shown in the table.

Conclusion A history of thyroid disease or thyroid hormone therapy is not associated with hip fracture in women aged 65 years or older.

COMMENTARY

These women had their fractures in the early 1970s. In their discussion, the authors say they chose this time "to maximize the likelihood of detecting an association between thyroid hormone use and fracture," but they do not say why. Did they think more women were being treated for hypothyroidism, or that overtreatment was more common then? The former is unlikely, because serum thyrotropin (TSH) assays had only recently become available, and therefore few women were given a diagnosis of subclinical hypothyroidism then. On the other hand, overtreatment was probably more common, because the serum TSH assays then in use were not sufficiently sensitive to distinguish between low and normal serum TSH values.

Another explanation for selection of that time interval might be that older women were more at risk for osteoporosis, and therefore hip fracture, because less attention was paid to bone loss and minimizing it, possibly making it easier to detect an effect of thyroid hormone on hip fracture.

That said, this case–control study adds to the evidence from both case–control and cohort studies that thyroid hormone therapy itself is not a risk factor for hip fracture (1-3). There is, of course, no reason to expect this treatment to be harmful unless the doses are high enough to cause hyperthyroidism. Women who take high doses, specifically doses sufficient to lower serum thyrotropin (TSH) concentrations to ≤0.1 mU/L, do have an increased risk of hip fracture (2). Thyroid hormone therapy that has this effect can be justified only in women with thyroid carcinoma who have a high risk of persistent or recurrent tumor.

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Papillary thyroid microcarcinomas grow very slowly

Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, Yokozawa T, Matsuzuka F, Kuma S, Kuma K, Miyauchi A. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 2003;13:381-7.

SUMMARY

Background Papillary thyroid carcinomas that are ≤1 cm in maximal diameter are called microcarcinomas. They are usually detected as an incidental nodule at the time of ultrasonography done to evaluate a larger nodule, and the diagnosis is established by fine-needle aspiration biopsy. This study was done to determine the growth rate of microcarcinomas in patients who declined surgery at the time of initial diagnosis.

Methods From 1993 to 2001, 732 patients with thyroid nodules ≤1 cm in maximal diameter detected mainly by ultrasonography and found on fine-needle aspiration biopsy to have the typical cytologic changes of papillary carcinoma were evaluated at a single center. Patients with tumors located near the trachea or a recurrent laryngeal nerve, those with lymph nodes thought to contain tumor, and those in whom the biopsy suggested high-grade carcinoma (criteria not stated) were advised to have immediate surgery. The remainder were offered two options—immediate surgery, or observation with periodic ultrasonography and repeat biopsy as indicated.

Results Among the 732 patients, 570 chose immediate surgery and 162 chose observation. In the latter group there were 157 women and 5 men (mean age, 52 years; range, 23 to 80). The mean (±SD) tumor diameter was 7±3 mm, 30 (18 percent) had other nodules suspicious for carcinoma, 11 (7 percent) had suspicious lymph nodes, and 107 (66 percent) had benign thyroid nodules.

During a mean a follow-up period of 46±22 months (range, 18 to 113), the size of the microcarcinoma did not change (as defined by an increase or decrease of <2 mm in maximal diameter) in approximately 65 percent of the patients, it increased by ≥2 cm in approximately 25 percent, and it decreased by ≥2 cm in approximately 10 percent (Table).

Table. Mean (±SD) Changes in Size of Papillary Microcarcinomas during Follow-up.

	No.	Size (mm)	Size Increased (n)	No Change (n)	Size Decreased (n)
Base line	162	7±2			
One year	130	7±2	20 (15%)	92 (71%)	18 (14%)
Three years	90	8±2	19 (21%)	61 (68%)	10 (11%)
Five or more years	58	7±2	16 (28%)	35 (60%)	7 (12%)

Among these 162 patients, 56 had surgery 19 to 56 months later. The tumor had increased in size in 13 patients (23 percent), decreased in 7 (13 percent), and not changed in 36 (64 percent). The indications for surgery were tumor size >10 mm in 7 patients, appearance of lymph node metastases in 2 patients, and patient choice or enlargement of benign nodules in the remainder. All the tumors proved to be papillary carcinomas on histologic evaluation. The surgical findings in these 56 patients were similar to those of the 570 patients who chose surgery at the time of diagnosis in terms of tumor size and extent. For example, 11 of the 56 patients (20 percent) had lymph node metastases, as compared with 110 of the 570 patients (19 percent).

During a mean postoperative follow-up period of 49 months (range 0 to 120), 16 of all 626 patients (3 percent) who were operated on had a recurrence. No patient died of papillary carcinoma.

Conclusion The majority of papillary microcarcinomas of the thyroid gland do not enlarge during the first five years after diagnosis.

COMMENTARY

When thyroid nodules that are purported to be papillary carcinomas do not grow, much less shrink, during follow-up, the first question that comes to mind is whether the diagnosis was wrong. However, the authors used accepted cytologic criteria for the diagnosis of papillary carcinoma, and the diagnosis was confirmed by histologic study in all the patients who had surgery, whether at the time of initial evaluation or later. Furthermore, during the same time period, another 2869 patients with thyroid nodules (presumably >1 cm in diameter) and a cytologic diagnosis of papillary carcinoma were operated on at the same hospital, and 2838 (99 percent) proved to have papillary carcinoma. Despite the cytologic and histologic similarity of the large and small carcinomas, there must be something fundamentally different about the carcinomas that are small when detected, and do not grow thereafter, and those that are larger when detected.

Thyroid nodules that are ≤1 cm in maximal diameter, whether detected by ultrasonography or, occasionally, by physical examination, are referred to as incidentalomas, and often are not biopsied. There is, of course, no reason to doubt that some are carcinomas, and that fact is certainly confirmed by this study. Given the more conservative policy of not performing biopsy of nodules ≤1 cm, microcarcinomas will not be detected, either at the time of initial ultrasonography or, in most patients, during follow-up (except as an incidental finding in a patient who has surgery for another reason). Furthermore, failure to detect them has almost no consequences. These facts lend support to a conservative biopsy policy, as does the fact that the proportion of nodules ≤1 cm that are benign is as high if not higher than is the proportion of nodules >1 cm that are benign (>90 percent in most studies).

Robert D. Utiger, M.D.

Differentiated thyroid carcinoma can be aggressive in elderly patients

Vini L, Hyer SL, Marshall J, A'Hern R, Harmer C. Long-term results in elderly patients with differentiated thyroid carcinoma. Cancer 2003;97:2736-42.

SUMMARY

Background Most patients with differentiated thyroid carcinoma are 30 to 60 years old, but both younger and older patients may be affected. This study was done to determine the clinical characteristics and course of patients aged 70 years and older with these tumors.

Methods The study subjects were 111 patients with differentiated thyroid carcinoma who were ≥70 years old at the time of diagnosis and who were followed for at least two years after completion of initial therapy at a single referral center in the United Kingdom. These patients constituted 8 percent of all patients with differentiated thyroid carcinoma seen there since 1949. The patients' records were reviewed for information about presentation, pathologic findings, treatment, and outcome.

Results There were 83 women (75 percent) and 28 men (25 percent); the median age was 75 years, and the oldest patient was 93 years old. The presenting manifestation of the tumor was a thyroid mass in 89 patients (80 percent), enlarged cervical lymph nodes in 17 patients (15 percent), and bone pain in 6 patients (5 percent). Fifty-eight patients (52 percent) had a papillary carcinoma, 46 (41 percent) follicular carcinoma, and 7 (6 percent) Hurthle-cell carcinoma; the tumor was considered well-differentiated in 55 patients (50 percent). The tumor was >4 cm in longest dimension or extended beyond the thyroid capsule in 78 patients (70 percent), lymph nodes were involved in 49 patients (44 percent), and distant metastases were detected in 26 patients (23 percent).

The primary treatment was total thyroidectomy in 46 patients (41 percent), subtotal thyroidectomy in 36 patients (33 percent), and biopsy only in 29 patients (26 percent). Subsequently, 22 patients (20 percent) received a single dose of 80 mCi (3000 MBq) iodine-131 (I-131), and 58 patients (52 percent) received multiple doses. Twenty-four patients (22 percent) were treated with external-beam radiation for local recurrence or palliation of pain from bone metastases.

During a median follow-up interval of 9 years (range, 2 to 19), 23 patients (21 percent) had a local recurrence and 17 patients (15 percent) had distant metastases; the median time to recurrence or metastasis was 9 months (range, 2 to 32). The overall survival rates were approximately 50 percent at 5 years and 25 percent at 10 years (extrapolated from Figure 1 of the paper). The tumor-related survival rates were 75 percent, 50 percent, and 50 percent at 5, 10, and 15 years, respectively.

In univariate analyses, older age (≥80 years), lymph node metastases, and external-beam radiotherapy were associated with a lower tumor-related survival rate, and follicular histology and total thyroidectomy with a higher tumor-related survival rate, as compared, respectively, with younger patients, those without those features, or those not treated in those ways. In multivariate analysis, the only determinants of a high tumor-related survival rate were age ≤80 years, absence of metastases, and no external-beam radiotherapy.

There was a statistically significant ($P<0.03$) increase in survival during the study interval; the median survival was 4.7 years before 1970, as compared with 6.0 years in the 1970s, 8.8 years in the 1980s, and >10 years in the 1990s. Total thyroidectomy and postoperative I-131 therapy became routine only during the 1990s.

Conclusion Among elderly patients, differentiated thyroid carcinomas tend to be large at the time of diagnosis and their course can be aggressive.

COMMENTARY

There is general agreement that the likelihood of recurrence and death from differentiated thyroid carcinoma is higher in older patients (1,2); in the authors' entire cohort of 1390 the risk of recurrence and death from thyroid carcinoma increased linearly with age. Older patients tend to have larger tumors at the time of diagnosis, and they are more likely to have lymph node and distant metastases, as compared with younger patients. There are several possible explanations for these differences. One is later diagnosis, because straightening of the cervical spine with age makes the thyroid less prominent, and therefore nodules are less likely to be seen and more difficult to palpate. Also, the increasing frequency of benign thyroid nodules with age may reduce the likelihood of investigation of nodules that are detected. Another is that older patients with thyroid carcinoma may not be treated as aggressively as are young patients, particularly with respect to surgery, because they are considered poor operative risks, whether because of comorbid conditions or age alone. Finally, the biology of the tumors may differ. For one thing, in this series the proportion of follicular carcinomas was considerably higher than is found among younger patients, although the authors do not provide separate outcome data for patients with papillary and follicular carcinoma. For another, the molecular abnormalities may differ, even among histologic types, such that the tumors in older patients are less differentiated and grow more rapidly.

Robert D. Utiger, M.D.

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Older age and greater tumor size and extent predict poor outcome in Hurthle-cell carcinoma

Lopez-Penabad L, Chiu AC, Hoff AO, Schultz P, Gaztambide S, Ordonez NG, Sherman SI. Prognostic factors in patients with Hurthle cell neoplasms of the thyroid. Cancer 2003;97:1186-94.

SUMMARY

Background Thyroid tumors composed largely of Hurthle cells are uncommon, and relatively little is known about the characteristics of these tumors and patient outcome. This retrospective study was done to determine the relationships between the clinical and pathologic features of Hurthle-cell tumors and prognosis.

Patient Characteristics and Treatment The study subjects were 38 patients with a Hurthle-cell adenoma and 89 patients with a Hurthle-cell carcinoma who received their initial treatment at a single center from 1944 to 1995. The pathologic diagnosis was confirmed by a single pathologist; benign and malignant tumors were distinguished on the basis of capsular or vascular invasion in sections of the primary tumor or the presence of metastases. Approximately 65 percent of the patients in both groups were women. The mean age at diagnosis in the adenoma group was 43 years, and it was 52 years in the carcinoma group.

The mean adenoma size was 2.9 cm (>4 cm in 6 patients [16 percent]) and that of the carcinomas was 4.3 cm (>4 cm in 39 patients [44 percent]). Most patients presented with a thyroid mass. However, among the patients with carcinoma, 8 (9 percent) presented with distant metastases; studies at that time revealed that 22 patients (25 percent) had lymph node metastases and 16 patients (18 percent) had distant metastases. Twenty-nine patients (33 percent) had multiple microscopic foci of carcinoma within the thyroid, and 7 patients (8 percent) had foci of anaplastic carcinoma within the Hurthle-cell carcinoma. Thirty-five patients (39 percent) in the carcinoma group underwent unilateral surgery and 54 (61 percent) bilateral surgery; 64 patients (72 percent) also received iodine-131 (I-131).

Among the patients with carcinoma, 37 were known to have lymph node or distant metastases, or both, when an I-131 scan was done. I-131 uptake was detected in the metastases in 14 of these patients (38 percent). Most of these metastases were in lymph nodes (9 of 12 patients [75 percent]). In contrast, I-131 uptake was detected in only 2 of 27 patients (7 percent) with lung metastases and in only 3 of 33 patients (9 percent) with bone metastases. Forty-three patients (48 percent) received external-beam radiotherapy.

Results The mean duration of follow-up was 9 years in the adenoma group and 10 years in the carcinoma group. No patient in the adenoma group died as a result of the tumor. In contrast, 36 patients (40 percent) in the carcinoma group died as result of the tumor (56 patients [63 percent] died overall). The 20-year tumor-related mortality rate, estimated by the Kaplan–Meier method, was 40 percent (extrapolated from Figure 4 of the paper). There was no change in overall or tumor-related mortality in the patients with Hurthle-cell carcinoma during the study period.

Forty-seven patients (53 percent) had progression of their disease after initial treatment. Factors associated ($P \leq 0.05$) with progression in univariate analyses were age >45 years, larger tumor size, extrathyroidal invasion, foci of anaplastic carcinoma, and local and distant metastases. These factors, more extensive surgery, and external-beam radiotherapy were associated with increased risk of tumor-related mortality. I-131 therapy had no overall effect; however, the mortality rate was lower in patients treated with I-131 for remnant destruction than in those treated for persistent or recurrent disease and those not treated with I-131. Tumor encapsulation was associated with decreased risk of progression, but not mortality; vascular invasion was not associated with either progression or mortality.

Conclusion Among patients with Hurthle-cell carcinoma of the thyroid those who are older, have large tumors, and have extensive disease at diagnosis are most likely to have disease progression and die of their disease.

COMMENTARY

These two studies provide complementary information about Hurthle-cell carcinomas. The patient and tumor characteristics associated with a poor prognosis were similar in the two studies. Lopez-Penabad et al. provide many more details about treatment and course, including capacity for I-131 transport. In contrast, Bhattacharyya provides data on more patients than anyone has studied previously, and provides unique data indicating that the prognosis is similar in patients with Hurthle-cell carcinoma and those with follicular carcinoma. This latter point has been debated for years, with some investigators suggesting that Hurthle-cell carcinomas are more aggressive than follicular carcinomas, but others finding no difference.

Hurthle cells are something of an enigma. They differ histologically from ordinary thyroid follicular cells in that they are stuffed with mitochondria. The factors responsible for this change, and how the change affects thyroid-cell function, are not known, but just about any thyroid follicular cell, whether in a benign or malignant tumor, a nodular goiter, Hashimoto's thyroiditis, or even Graves' disease, can acquire the characteristics of Hurthle cells. Hurthle-cell tumors, by definition, contain at least 75 percent Hurthle cells. Some benign and malignant Hurthle-cell tumors transport iodine and produce thyroglobulin (1), as in all likelihood do nontumor Hurthle cells.

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Mortality is similar among patients with Hurthle-cell carcinoma and follicular carcinoma

Bhattacharyya N. Survival and prognosis in Hurthle cell carcinoma of the thyroid gland. Arch Otolarygngol Head Neck Surg 2003;129:207-10.

SUMMARY

Background Hurthle-cell carcinomas of the thyroid are distinct tumors, although related to follicular carcinomas. The clinical and pathologic determinants of prognosis in patients with Hurthle-cell carcinomas are not well defined, and there is debate at to whether the prognosis in patients with Hurthle-cell carcinoma differs from that of patients with follicular carcinoma. In this retrospective study the clinical and pathologic features of Hurthle-cell carcinoma and prognosis were determined in a national cohort of patients, and the results compared with those of a matched cohort of patients with follicular carcinoma.

Patient Selection and Characteristics All cases of Hurthle-cell carcinoma entered in the Surveillance, Epidemiology and End Results (SEER) database between 1973 and 1998 were reviewed. This database contains cancer incidence and survival data from 11 population-based cancer registries throughout the U.S. Among 20,025 patients with thyroid carcinoma recorded in this database during this interval, 602 (3.0 percent) had a Hurthle-cell carcinoma. Forty-seven patients were excluded because they had distant metastases or incomplete information about extent of disease at the time of diagnosis, leaving 555 patients.

There were 377 women (68 percent) and 178 men (32 percent), with a mean age at diagnosis of 56 years. The mean tumor size was 3.5 cm; 465 patients (84 percent) had only thyroid disease, 62 (11 percent) had minor local extension (tumor invasion of adjacent tissue), 20 (4 percent) had major local invasion (tumor invasion of the carotid sheath, sternomastoid muscle, or larynx), and 8 (1 percent) had extravisceral extension (tumor invasion of the trachea, paravertebral muscles, or vertebrae). Cervical lymph nodes were resected at the time of initial treatment in 103 patients, of whom 15 (14 percent) had nodes positive for tumor. No other information about treatment is included.

The outcome in 411 of the patients with Hurthle-cell carcinoma was compared with that of 411 patients with follicular carcinoma matched for age, sex, tumor size, extent of local extension, and year of diagnosis. The Kaplan–Meier method was used to estimates survival rates.

Results In the patients with Hurthle-cell carcinoma, male sex and larger tumor size, but not local invasion, were associated with increased overall mortality (hazard ratios, 1.02 to 2.68). The 10-year mortality rate was approximately 20 percent in women and 45 percent in men; it was approximately 25 percent in patients with tumor limited to the thyroid, 33 percent in patients with minor local invasion, 65 percent in patients with major local invasion, and 68 percent in patients with extravisceral extension. (All these percentages were extrapolated from Figures 3 and 4 of the paper.)

The actuarial 5- and 10-year overall mortality rates in the patients with Hurthle-cell carcinoma were 15 percent and 29 percent, respectively, as compared with 11 percent and 45 percent, respectively, in the matched patients with follicular carcinoma. The mean survival time in the patients with Hurthle-cell carcinoma was 109 months (95 percent confidence interval, 105 to 114 months), as compared with 113 months (95 percent confidence interval, 109 to 118 months) in the patients with follicular carcinoma (P=0.47).

Conclusion Among patients with Hurthle-cell carcinoma, male sex, older age, large tumor size, and major extension are poor prognostic factors. The overall mortality rate is similar among patients with Hurthle-cell carcinoma and matched patients with follicular carcinoma.

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The distinction between benign and malignant Hurthle-cell tumors is based on the presence or absence of capsular and vascular invasion, as is the case for follicular tumors, and Hurthle-cell carcinomas have been considered as a subtype of follicular carcinoma, although they are now considered distinct tumors.

Recently, some Hurthle-cell carcinomas have been found to have the rearrangements in the *ret/PTC* gene and also some of the biologic characteristics, for example lymph-node metastases, that are more characteristic of papillary carcinomas than follicular carcinomas (2).

What this suggests is that papillary-carcinoma cells and follicular-carcinoma cells, as well as benign follicular adenomas and thyroid follicular cells in other benign thyroid conditions, may acquire the Hurthle-cell phenotype The existence of two types of Hurthle-cell carcinomas, one type with the biologic characteristics of papillary carcinomas and the other type with the characteristics of follicular carcinomas, might explain the varying prognosis of patients with Hurthle-cell carcinoma reported in different studies.

Robert D. Utiger, M.D.

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Patient and tumor characteristics are similar in patients with pure papillary carcinoma or follicular variant of papillary carcinoma

Zidan J, Karen D, Stein M, Rosenblatt E, Basher W, Kuten A. Pure versus follicular variant of papillary thyroid carcinoma. Clinical features, prognostic factors, treatment, and survival. Cancer 2003;97:1181-5.

SUMMARY

Background There are two major subtypes of papillary carcinoma of the thyroid, so-called pure papillary carcinoma and follicular variant of papillary carcinoma. The latter has been recognized with increasing frequency in recent years, but whether its biology is similar to that of pure papillary carcinoma is not clear. In this retrospective study the characteristics and outcome of patients with the two subtypes were compared.

Methods The study subjects were 243 patients with papillary carcinoma treated at a single oncology center in Israel between 1972 and 1990. Sections of all tumors were reviewed by several pathologists. The tumor was classified as a pure papillary carcinoma if it was composed of papillae lined by cells with nuclei that were enlarged and overlapped one another, and the nuclei had a thick nuclear membrane, small nucleoli next to the nuclear membrane, intranuclear grooves, and intranuclear inclusions. The tumor was classified as a follicular variant of papillary carcinoma if it was composed primarily of follicles (80 percent or more) and the nuclei of the cells had at least two of the features of papillary carcinoma. All patients had undergone total or near-total thyroidectomy, and 226 patients in whom postoperative imaging revealed uptake of iodine-131 (I-131) received a therapeutic dose of I-131; later treatment varied according to the presence and site of recurrence.

Results There were 143 patients (59 percent) with pure papillary carcinoma and 100 patients (41 percent) with follicular variant of papillary carcinoma. There were no differences in the characteristics of the patients or the tumors in the two groups (Table 1).

Table 1. Clinical and Pathologic Characteristics in Patients with Two Types of Papillary Carcinoma.

	Pure Papillary (n=143)	Follicular Variant (n=100)
Age - mean yr (range)	43 (11-78)	44 (17-81)
Women/men	94/49	74/26
Tumor size - mean cm (range)	3.2 (0.4-9.0)	3.5 (0.3-10.0)
Tumor stage		
Stage I	96 (67%)	69 (69%)
Stage II-III	35 (25%)	24 (24%)
Stage IV	12 (8%)	7 (7%)
Multifocal intrathyroidal tumor	36 (25%)	33 (33%)
Capsular invasion	44 (31%)	38 (38%)
Lymph node metastases at diagnosis	46 (32%)	22 (22%)
Distant metastases at diagnosis	13 (9%)	8 (8%)

The median follow-up was 138 months (range, 48 to 288). The overall actuarial 21-year survival rates were, respectively, 82 percent in the patients with pure papillary carcinoma and 86 percent in the patients with the follicular variant of papillary carcinoma. Among several prognostic factors, only age was a determinant of poor outcome in either group ($P<0.01$ in both groups), but there was no difference between groups (Table 2).

Table 2. Actuarial 21-Year Survival of Patients with Two Types of Papillary Carcinoma.

Age at Diagnosis - yr	Pure Papillary	Follicular Variant
<40	100%	97%
40-50	95%	88%
>50	51%	71%

Conclusion Patients with pure papillary carcinoma and follicular variant of papillary carcinoma do not differ in age, sex, or extent of tumor at the time of diagnosis, nor is their prognosis different.

COMMENTARY

Papillary carcinomas are usually subdivided into papillary carcinomas and follicular variants of papillary carcinoma, which are common, and the rare sclerosing papillary carcinomas, tall-cell papillary carcinomas, and columnar-cell papillary carcinomas. In the World Health Organization Classification of Tumours (1), papillary carcinoma is described as "A malignant epithelial tumour showing evidence of follicular cell differentiation, typically with papillary and follicular structures as well as characteristic nuclear changes." Follicular variants of papillary carcinoma, in contrast, are composed almost entirely of follicles, but the cell nuclei have the characteristic features of papillary carcinoma.

In keeping with this definition, Zidan et al. classified thyroid carcinomas as follicular variant of papillary carcinoma when at least 80 percent of the tumor had a follicular architecture, but they required only two of the nuclear features of papillary carcinoma (as listed in the summary above). The lack of requirement for more, if not all, of the nuclear changes characteristic of papillary carcinoma may explain the large number of cases of follicular variant of papillary carcinoma relative to the number of cases of papillary carcinoma in their series (100 vs. 143, 41 percent of the total). This also highlights the fact that there is no agreement as to the number of nuclear changes or proportion of nuclei affected that must be seen to say that a tumor is a follicular variant of papillary carcinoma, or even a papillary carcinoma. And there is as yet no molecular or other marker that correlates with the presence of the typical nuclear changes of papillary carcinoma.

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A low-iodine diet increases the efficacy of initial iodine-131 therapy in patients with thyroid carcinoma

Pluijmen MJ, Eustatia-Rutten C, Goslings BM, Stokkel MP, Arias AM, Diamant M, Romijn JA, Smit JW. Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma. Clin Endocrinol 2003;58:428-35.

SUMMARY

Background Many patients with thyroid carcinoma are treated with iodine-131 (I-131) after surgery to destroy both any remaining normal thyroid tissue and thyroid carcinoma. The efficacy of I-131 therapy for remnant destruction may be increased by dietary iodine restriction before I-131 administration. In this retrospective study the ability of I-131 to destroy thyroid remnants was compared in patients who ate a low-iodine diet or their usual diet before the administration if I-131.

Methods The study subjects were 120 patients (94 women, 26 men; mean [±SD] age, 43±15 years) with papillary or follicular carcinoma who underwent near-total thyroidectomy at a single hospital from 1986 to 1998. Patients with metastatic disease, those who had undergone only subtotal thyroidectomy or had serum thyrotropin (TSH) concentrations <25 mU/L, and those asked to follow a low-iodine diet whose urinary iodine excretion was >49 µg/day (0.39 mmol/day) were excluded (the number of patients in each of these groups is not stated).

Four weeks after surgery 24-hour I-131 uptake was measured after administration of 1 mCi (37 MBq) of I-131. The patients were then treated with an average of 76 mCi (2800 MBq) I-131 (range not stated). Those patients treated from 1986 to 1991 ate their usual diet, whereas those treated from 1992 to 1998 ate a diet designed to reduce urinary iodine excretion to ≤49 µg/day (0.39 mmol/day) for four days before I-131 administration. The patients were then treated with thyroxine (T_4). Six months later, the T_4 was stopped, and a whole-body scan was done three days after administration of 5 mCi (185 MBq) of I-131. All patients ate a low-iodine diet for four days before the second I-131 study. Serum TSH, T_4, and thyroglobulin, and urinary iodine were measured at the time of both I-131 studies.

Results There were 59 patients in the low-iodine diet group and 61 patients in the usual diet group. The clinical characteristics of the patients, including tumor histology and stage, in each of the two groups were similar. The patients in the low-iodine diet group had a higher thyroid I-131 uptake before I-131 treatment, and at the time of the second study they had more severe hypothyroidism and were more likely to have no uptake and a low serum thyroglobulin concentration (Table).

Table. Effects of Low-Iodine and Usual Diets on Serum Hormone and Thyroid I-131 Uptake in Patients with Thyroid Carcinoma.

	Low-Iodine Diet Group	Usual-Diet Group	P Value
First I-131 Study			
Urinary iodine (µg/day)	27±12	159±9	<0.01
Serum TSH (mU/L)	80±38	73±39	0.30
Serum T_4 <1.0 µg/dl (%)	41	24	0.06
Serum thyroglobulin <2 µg/L (%)	34	38	0.73
24-Hour neck uptake (%)	5±4	3±3	<0.01
Uptake in neck (%)	100	100	1.00
Second I-131 Study			
Urinary iodine (µg/day)	25±10	28±10	0.19
Serum TSH (mU/L)	106±51	84±48	0.02
Serum T_4 <1.0 µg/dl (%)	94	62	<0.01
Serum thyroglobulin <2 µg/L (%)	85	69	0.07
No uptake in neck (%)	67	73	0.56
No uptake and serum thyroglobulin <2 µg/L (%)	65	48	<0.01

Values are means (±SD). To convert urinary iodine values to µmol/day, multiply by 0.008; and to convert serum T_4 values to nmol/L, multiply by 12.9.

Conclusion Thyroid remnants in patients with thyroid carcinoma are more likely to be destroyed by I-131 if the patients eat a low iodine diet before I-131 administration.

COMMENTARY

Most patients with thyroid carcinoma who are to be treated with I-131 are asked to follow a low-iodine diet for up to two weeks before being given I-131. Reducing iodine intake would be expected to deplete the extracellular iodine pool, so that when I-131 is given the proportion of iodine in the pool that is I-131, and therefore the proportion taken up by thyroid tissue—whether normal or tumor tissue—is higher than it would be if the pool had not been depleted. In addition, iodine deficiency may increase the production of iodine transporters in thyroid cells, both directly and by raising serum TSH concentrations, which should also increase iodine uptake

Pluijmen et al. found that patients who ate a low-iodine diet for only four days had a low urinary iodine excretion and more I-131 uptake into thyroid tissue remaining after surgery, and more importantly that the remnant was more likely to be destroyed by a therapeutic dose of I-131. This is, after all, the reason the treatment is given. The study was not randomized, and the exact doses of I-131 given for remnant destruction are not stated, so the low-iodine diet may have been less effective than seems at first glance. Although some have found that restricting dietary iodine intake before I-131 therapy does not increase the efficacy of therapy (1), its physiological basis is sound, and it is often advised. Since some patients find a low-iodine diet uninviting, what is needed now is detailed information about how long iodine intake needs be restricted.

Robert D. Utiger, M.D.

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Late recurrence and late hypothyroidism are rare in subacute granulomatous thyroiditis

Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab 2003;88:2100-5.

SUMMARY

Background Subacute granulomatous thyroiditis, also called de Quervain's thyroiditis, is a distinctive type of thyroid inflammation characterized by thyroid pain and tenderness, nonspecific symptoms of inflammation, and transient hyperthyroidism and hypothyroidism. This study was done to determine the characteristics and outcome of subacute granulomatous thyroiditis in a cohort of patients living in a defined geographic area.

Methods Cases of subacute granulomatous thyroiditis (hereafter referred to as subacute thyroiditis) were identified from the records of the Mayo Clinic (1960 to 1997) and the Rochester Epidemiology Project (1966 to 1997). These records contain comprehensive medical information about virtually all residents of Olmsted County, Minnesota. The inclusion criteria were thyroid pain and a low thyroid radioiodine uptake or high erythrocyte sedimentation rate; unilateral thyroid pain and a low thyroid radioiodine uptake and a high erythrocyte sedimentation rate; or a pathologic diagnosis of the disorder. The patients' records were reviewed through 1997, and telephone interviews were conducted if no recent information was available.

Results There were 160 cases of subacute thyroiditis between 1960 and 1997. The age-adjusted annual incidence rate declined from 8.7 cases/100,000 people in the 1960s to 3.2 cases/100,000 in the 1980s and 3.6/100,000 in the 1990s. Cases were evenly distributed throughout the year, and there was never more than one case per household.

The clinical features were evaluated in the 94 cases encountered between 1970 and 1997. There were 73 women and 21 men, mean age, 46 years (range, 14 to 87). Twenty patients (21 percent) had a history of an upper respiratory infection during the 30 days before the onset of thyroiditis. Ninety-one patients (97 percent) of the patients had mild to severe thyroid pain; the pain radiated to the jaw in 12 patients (13 percent) and to the ears in 18 patients (19 percent). Thirty patients (32 percent) had dysphagia, 15 (16 percent) had myalgia or arthralgia, and 15 (16 percent) had weight loss. Seven of 41 patients (17 percent) were febrile. Eighty-nine of the 94 patients (95 percent) had thyroid tenderness; it was bilateral in 44, unilateral in 31, and not stated in the remainder. Thyroid weight, estimated in 78 patients, was <20 g in 19 patients and between 20 and 70 g in 57 patients. Mean (±SD) test results were: serum free thyroxine; 2.8±2.0 ng/dl (36±26 pmol/L); serum triiodothyronine, 180±75 ng/dl (2.8±1.2 nmol/L); serum thyrotropin (TSH), 0.9±1.6 mU/L; thyroid radioiodine uptake, 3.2±3.5 percent; and erythrocyte sedimentation rate, 51±26 mm/hr (these tests were done in 11 to 84 percent of patients).

Among the 94 patients, 15 (16 percent) received prednisone, 39 (41 percent) received a nonsteroidal antiinflammatory drug (mostly acetylsalicylic acid), 18 (19 percent) received both, and 21 (22 percent) received acetaminophen. High doses of prednisone (30 to 40 mg/day) were given for 4 to 43 days, and it was continued for a mean of 43 days. The mean time to resolution of thyroid pain was four days in the patients treated with prednisone and 35 days in those treated with a nonsteroidal antiinflammatory drug. Eleven patients were treated with a beta-adrenergic antagonist drug.

Nine patients (10 percent) had a recurrence of symptomatic thyroiditis within 6 to 12 months, and 4 patients (4 percent) had a recurrence 6 to 21 years later. Twenty-seven patients (29 percent) had a high serum TSH concentration in the first year after diagnosis, of whom 9 were being treated with thyroxine at last follow-up. Hypothyroidism occurred 2 to 24 years later in 5 patients (5 percent). At last follow-up (maximal duration, 28 years), 14 patients (15 percent) had hypothyroidism; 8 had received prednisone and 6 had received a nonsteroidal antiinflammatory drug. One patient had undergone thyroidectomy for persistent thyroid pain.

Conclusion Among patients with subacute thyroiditis, early recurrence and transient hypothyroidism are relatively common, but late recurrence and permanent hypothyroidism are rare.

COMMENTARY

Subacute granulomatous thyroiditis is considered a viral disorder, but the evidence for this is largely circumstantial. That evidence includes the following: an upper respiratory infection that is presumably viral in origin may precede the thyroiditis; fever, myalgia and arthralgia often accompany it; and thyroid biopsies reveal thyroid inflammation and granulomas. But the causative virus(es) has remained elusive.

Transient hypothyroidism (and a transient rise in serum viral [or thyroid] antibody concentrations) may occur after any type of thyroid injury. Indeed the frequency of transient hypothyroidism may have been underestimated in this study because the patients were not studied systematically. Early recurrence is likely recrudescence of the same insult (?infection), whereas late recurrence is probably a new insult (?infection). But the facts of early and late recurrences do not really provide much insight into the cause(s) of the disorder.

Robert D. Utiger, M.D.

The frequency of autoimmune thyroid disease increases with time in type 1 diabetes mellitus

Hansen D, Bennedbaek FN, Hoier-Madsen M, Hegedus L, Jacobsen BB. A prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 diabetes. Eur J Endocrinol 2003;148:245-51.

SUMMARY

Background Patients with type 1 diabetes mellitus are at increased risk of chronic autoimmune thyroiditis, as detected by measurements of serum antithyroid antibodies or thyroid ultrasonography, but there has been little follow-up study of thyroid autoimmunity and morphology in these patients. In this study these tests were repeated in a group of children and adolescents with type 1 diabetes three years after initial study.

Methods In 1997, serum antithyroid antibodies, thyrotropin (TSH), and thyroxine (T_4) were measured and thyroid ultrasonography was done in 105 children and adolescents with type 1 diabetes (91 percent of all young people with diabetes in one county in Denmark) and 105 age- and sex-matched normal subjects. In 2000, these tests were repeated in 101 (96 percent) of the diabetic children and adolescents (47 girls, 54 boys; median age, 16 years [range, 5 to 21]; median duration of diabetes, 8 years [range, 3 to 16]). The investigators who performed the follow-up ultrasonography did not know the results of the initial study.

Results Five of the 101 patients with diabetes (5 percent) had overt or subclinical hypothyroidism when first studied; at follow-up three more patients had hypothyroidism (overt hypothyroidism, three patients; subclinical hypothyroidism, five patients). Four of these eight patients had a high serum antithyroid peroxidase antibody concentration, three had a high serum antithyroglobulin antibody concentration, and all eight had hypoechogenicity on thyroid ultrasonography.

At base line, 13 patients (13 percent) had a high serum antithyroid peroxidase antibody concentration. At follow-up, the concentration was higher in 10 patients and lower (but still high) in three patients. Fourteen patients (14 percent) had a high serum antithyroglobulin antibody concentration at base line, of whom seven had a high concentration at follow-up (all seven had a high serum antithyroid peroxidase antibody concentration). No patient who had a normal serum concentration of either antibody at base line had a high concentration at follow-up.

The median thyroid volume in the patients at base line was 9 ml (range, 2 to 23), as compared with 9 ml (range, 1 to 18) in the normal subjects. At follow-up, it was 11 ml (range, 3 to 34) ($P<0.01$), and was correlated with age and weight. Some ultrasonographic abnormality was detected in 42 patients (42 percent) at base line and in 49 patients (48 percent) at follow-up (Table); 33 (33 percent) had some abnormality at both times, 16 changed from normal to abnormal, and 9 changed from abnormal to normal. Ultrasonography was abnormal in 77 percent of patients with high serum antithyroid antibody concentrations and 44 percent of those with normal concentrations ($P=0.04$).

Table. Results of Ultrasonography at Base Line in Normal Subjects and at Base Line and Follow-Up in Patients with Diabetes.

	Normal Subjects (n=101)	Patients with Diabetes (n=101)	
	Base Line	Base Line	Follow-up
Normal thyroid	90%	58%	52%
Mild to moderate hypoechogenicity	3%	23%	33%
Marked hypoechogenicity	1%	4%	3%
Heterogeneous hypoechogenicity	3%	13%	8%
Nodules	3%	2%	5%

Conclusion Biochemical, serologic, and ultrasonographic abnormalities indicative of chronic autoimmune thyroiditis are common in children and adolescents with type 1 diabetes, and their frequency increases with time.

COMMENTARY

In this cohort, originally studied in 1997 (1), the intensity of thyroid autoimmune disease, as measured by serum antithyroid antibodies, both increased and decreased with time in individual patients, but there were no new cases during the three-year follow-up period.

As measured by ultrasonography, however, there were some new cases. The ultrasonographic finding of diffuse hypoechogenicity is to some extent subjective, and even if unequivocal it is not specific for autoimmune thyroiditis, but these young patients are not likely to have the other causes of hypoechogeneicity (other types of thyroiditis, Graves' disease, other thyroid infiltrative disorders). As a practical matter, patients with type 1 diabetes should have periodic measurements of serum TSH, but not serum thyroid antibodies and certainly not ultrasonography.

Why are patients with type 1 diabetes at increased risk for autoimmune thyroiditis? It seems unlikely that hyperglycemia or any related metabolic abnormality induces or exacerbates autoimmune thyroiditis, but a possible contribution from these factors has not been excluded. More likely, the same genetic factors determine susceptibility to the two disorders, although the inciting events and rates of progression differ.

Robert D. Utiger, M.D.

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The fasting-induced decline in serum thyrotropin, but not triiodothyronine, is blunted by leptin administration

Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest 2003;111:1409-21.

SUMMARY

Background Leptin is a product of adipose tissue that inhibits energy intake and increases energy expenditure. Its production decreases during starvation, and this decrease may mediate not only the metabolic but also the hormonal adaptations that limit the deleterious effects of starvation. This study was designed to determine the effects of the administration of leptin to normal subjects during starvation.

Methods The study subjects were six young, normal-weight men. They were studied (at ≥7-week intervals) while eating a normal diet and during 3-day fasts during which they received a low dose of leptin, a replacement dose of leptin, or placebo. The low dose of leptin varied from 0.001 to 0.008 mg/kg/day, according to the man's base-line serum leptin concentration. The replacement dose was 0.04 mg/kg on day 1, 0.1 mg/kg on days 2 and 3, and 0.025 mg/kg once on day 4; this regimen was designed to compensate for the progressive fall in serum leptin concentrations that occurs during fasting. The leptin was given subcutaneously, four times on days 1 to 3 and once on day 4.

Weight, resting metabolic rate, nutrient utilization, and serum leptin and other hormones were measured at the start and on day 3 or 4 of each study period. On day 3, serum thyrotropin (TSH), luteinizing hormone (LH), growth hormone (GH), and cortisol were measured every 15 minutes for 24 hours, and their circadian and pulsatile patterns of secretion were calculated.

Results The mean serum leptin concentration did not change during the normal diet. It decreased from 2.2 to 0.3 ng/ml on day 4 of the fasting study and from 1.9 to 0.5 ng/ml on day 4 of the fasting plus low-dose leptin study, and it increased from 3.4 to 7.4 ng/ml on day 4 of the fasting plus replacement-dose leptin study. During all three fasting studies, independent of leptin administration, the men lost approximately 2 kg, and their resting metabolic rate increased by approximately 250 kcal/day. The mean serum total and free thyroxine concentrations did not change during any study, except for a small increase in serum free thyroxine during the fasting plus replacement-dose leptin study. The mean serum triiodothyronine concentration decreased by approximately 30 percent during each fasting study, independent of leptin administration. For example, the mean serum triiodothyronine concentration was 69 ng/dl (1.1 nmol/L) before and 52 ng/dl (0.8 nmol/L) at the end of the fasting study, and it was 73 ng/dl (1.1 nmol/L) before and 45 ng/dl (0.7 nmol/L) ($P<0.01$) at the end of the fasting plus replacement-dose leptin study. During day 3 of fasting, there was a reduction in mean 24-hour serum TSH concentration, TSH secretion per pulse, and the integrated area under the serum TSH curve, but no change in TSH pulse frequency; the decreases were partially restored during leptin administration (Table).

Table. Characteristics (Mean±SE) of TSH Secretion during Feeding, Fasting and Fasting plus Leptin Administration.

	Fed	Fast	Fast + Low-Dose Leptin	Fast + Replacement-Dose Leptin	P Value
Mean serum TSH (mU/L)	1.0±0.3	0.3±0.04	0.4±0.06	0.6±0.09	0.02
Pulse frequency (no/24 hr)	16±1	14±1	15±1	15±2	0.83
TSH/pulse (mU/L)	1.1±0.3	0.3±0.05	0.3±0.05	0.7±0.09	<0.01
Area under serum TSH curve (mU/L)	1485±43	1428±61	504±80	867±132	0.02

The mean 24-hour serum LH concentrations, LH pulse frequency, the integrated area under the curve of LH secretion, and serum testosterone concentrations decreased during fasting, and the decreases were reversed by replacement-dose leptin administration. There were no changes in serum GH or cortisol concentrations during fasting or fasting plus leptin administration. Serum insulin-like growth factor 1 concentrations decreased during all three fasting studies.

Conclusion Administration of leptin blunts the decrease in TSH secretion but not the fall in serum triiodothyronine concentrations induced by fasting.

COMMENTARY

Fasting affects hypothalamic-pituitary-thyroid function in two ways, by reducing TSH secretion and by reducing the extrathyroidal production of triiodothyronine. The latter is the better-known change, and it cannot be attributed to leptin deficiency.

The decrease in TSH secretion seems to result primarily from a decrease in the amplitude of pulses of TSH secretion, especially at night when the pulse amplitude is greatest. The proximate cause of the decrease in TSH secretion is probably a decrease in hypothalamic secretion of thyrotropin-releasing hormone. The leptin-replacement study, which in fact raised serum leptin concentrations to well above those found during feeding, did not fully restore TSH secretion to normal. Therefore, decreased leptin production is not the sole cause of the fasting-related decrease in TSH secretion.

Persistence of the decrease in TSH secretion found on day 3 during prolonged fasting would be expected to result in a fall in serum thyroxine concentrations and hypothyroidism. This does not occur, because the stimulatory effect of low serum thyroxine concentrations on TSH secretion overrides the inhibition of TSH secretion induced by any nonthyroid stimuli that inhibit TSH secretion.

Robert D. Utiger, M.D.

Low serum free triiodothyronine values predict mortality in patients with cardiac disease

Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L. Low-T_3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation 2003;107:708-11.

SUMMARY

Background Many patients with nonthyroidal illness have abnormalities in pituitary-thyroid function, most commonly low serum triiodothyronine (T_3) concentrations. The physiological consequences of the decrease in serum T_3 concentrations are not known. This study assessed the relationships between serum T_3 concentrations and mortality in a large group of patients with cardiac disease.

Methods The study subjects were 573 consecutive patients hospitalized for diagnosis and treatment of cardiac diseases during a one-year period. Among the 573 patients, 129 had a cardiomyopathy, 51 an acute myocardial infarction, 91 a previous myocardial infarction, 189 myocardial ischemia, 60 an arrhythmia, and 53 valvular heart disease, myocarditis, and other cardiac disorders. One hundred fifty-eight patients were taking a beta-adrenergic antagonist drug, 150 an angiotensin-converting-enzyme inhibitor, and 84 amiodarone. Patients who had undergone coronary revascularization or other cardiac surgery, or who underwent these procedures in the six months after admission, and patients with overt thyroid disease were excluded.

In all patients serum thyrotropin (TSH), total and free thyroxine (T_4), and total and free T_3 were measured two to five days after admission. The patients were divided into two groups, those with low serum free T_3 concentrations (<0.20 ng/dl [3.1 pmol/L]) and those with normal concentrations (0.20 to 0.42 ng/dl [3.1 to 6.5 pmol/L]). Patient outcome was determined from patient records, interviews, examinations, and review of death certificates. Death was considered to be of cardiac origin if the patient died of major arrhythmia, cardiac arrest, congestive heart failure, or myocardial infarction.

Results The serum free T_3 concentration was low in 173 patients (30 percent) and normal in 400 patients (70 percent) (Table); the serum total T_3 concentrations were low and normal, respectively, in all patients with low and normal serum free T_3 concentrations. The patients in the low serum free T_3 group had a slightly lower left ventricular ejection fraction, and more of them had New York Heart Association class III–IV symptoms (84 vs. 70 percent, P=0.02). Among the 84 patients taking amiodarone, 16 (19 percent) had low serum free T_3 concentrations. Only 11 patients (2 percent) had low serum free T_4 concentrations.

Table. Left Ventricular Ejection Fraction and Serum T_3, T_4, and TSH Concentrations in Patients with Cardiac Disorders.

	Serum T_3 Low (n=173)	Serum T_3 Normal (n=400)	P Value
Left ventricular ejection fraction (%)	46%	49%	0.03
Serum free T_3 (ng/dl)	0.16±0.04	0.26±0.05	<0.001
Serum total T_3 (ng/dl)	60±19	99±19	<0.001
Serum free T_4 (ng/dl)	1.3±0.4	1.3±0.4	>0.05
Serum total T_4 (µg/dl)	8.1±5.6	9.0±2.4	0.007
Serum TSH (mU/L)	2.4±3.1	1.8±2.0	0.008

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

The 573 patients were followed for a mean (±SD) of 11±12 months. There were 13 cardiac deaths (7 percent) in the low serum free T_3 group and 6 cardiac deaths (2 percent) in the normal serum free T_3 group (P<0.001); overall, there were 25 deaths in the low serum free T_3 group (14 percent) and 12 deaths (3 percent) in the normal serum free T_3 group (P<0.001). Kaplan–Meier plots of survival versus time revealed an 11 percent difference in mortality in 30 days and a 17 percent difference at one year. A low serum free T_3 concentration was as or more strongly predictive of both cardiac and overall death than older age or a low left ventricular ejection fraction.

Conclusion Among patients with cardiac diseases who are hospitalized, a low serum T_3 concentration is a strong predictor of both one-month and one-year mortality.

COMMENTARY

In this study thyroid function was assessed once in patients with multiple cardiac disorders at a variable time after admission. Data are given relating serum T_3 values to left ventricular ejection fraction and NYHA symptom level, but the overall level of illness must have been moderate, given the rather low frequency of low serum T_3 concentrations, the rarity of low serum free T_4 values, and the low death rate. The number of patients admitted to an intensive care unit is not stated, nor is the frequency of low serum T_3 values and the mortality rates in the larger subgroups. The heterogeneity of the patients was such that identifying risk factors for death might be difficult, especially because the death rate was low.

Given these considerations, is the finding that low serum T_3 concentrations were predictive of a poor prognosis a chance observation, or a real finding? It is probably the latter. In other studies of patients hospitalized for heart failure, acute myocardial infarction, and different acute illnesses, the short- and long-term (up to one year) death rates were higher in those with low serum T_3 values. The question then becomes, does a low serum T_3 concentration mean that there is tissue T_3 deficiency that should be reversed, or is it simply an indicator, but not a cause, of severe tissue malfunction. If the former, treatment should be beneficial, otherwise not. At the least, these results suggest that a decrease in serum T_3 concentration may not be a beneficial adaptation to illness; otherwise low serum T_3 concentrations might be predictive of increased survival.

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The left thyroid lobe is missing in thyroid hemiagenesis

Maiorana R, Carta A, Floriddia G, Leonardi D, Buscema M, Sava L, Calaciura F, Vigneri R. Thyroid hemiagenesis: prevalence in normal children and effect on thyroid function. J Clin Endocrinol Metab 2003;88:1534-6.

SUMMARY

Background Agenesis of one lobe of the thyroid gland is thought to be a rare anomaly, but most of what is known about it has come from studies in which patients had a thyroid imaging procedure because they were thought to have a thyroid disorder. In this study the frequency of thyroid hemiagenesis was determined in a population-based cohort of children.

Methods Between 1999 and 2001, 24,032 children (12,280 girls, 11,752 boys) aged 11 to 14 years attending primary school in Sicily underwent thyroid ultrasonography as part of a survey of iodine nutrition. The length, depth, and width of each lobe of the thyroid were measured, and the volume was calculated as the volume of an ellipsoid ($\pi/6 \times$ length $\times$ depth $\times$ width). Thyroid hemiagenesis was defined as complete absence or marked hypoplasia (volume <10 percent of that of a normal lobe of a child of the same age) of a thyroid lobe. In those children with hemiagenesis, the volume of the lobe that was present was compared with the total volume and half the total volume of the thyroid in normal children of the same age. Serum free thyroxine (T_4), free triiodothyronine (T_3), and thyrotropin (TSH) were measured in most of the affected children and 18 age- and sex-matched normal children.

Results Twelve of the 24,032 children (0.05 percent) were found to have thyroid hemiagenesis. Seven were boys (1:1678; 0.06 percent) and five were girls (1:2456; 0.04 percent). The frequency was similar in children living in iodine-deficient and iodine-sufficient areas. Eleven children had complete absence of the left thyroid lobe, and one had severe hypoplasia of the left lobe (volume, 0.8 ml). Whether the isthmus was also missing is not stated. Among these 12 children, the volume of the remaining lobe was similar to the mean (±1SD) total volume in normal children of the same age in 4 (33 percent), larger in 3 (25 percent), and smaller in 5 (42 percent). In only 1 child was the volume of the remaining lobe less than half the total volume in normal children.

All nine children in whom thyroid function was assessed had serum TSH, free T_4, and free T_3 concentrations within their respective normal ranges. However, the children's mean serum TSH and free T_3 concentrations were higher than in the 18 age-matched normal children (Table).

Table. Serum TSH, Free T_4, and Free T_3 Concentrations in Children with Thyroid Hemiagenesis and Normal Children.

	Children with Hemiagenesis (n=9)	Normal Children (n=18)	P Value
Serum TSH (mU/L)	2.8±0.6	1.9±0.5	<0.01
Serum free T_4 (ng/dl)	1.1±0.2	1.1±0.2	0.78
Serum free T_3 (ng/dl)	0.4±0.05	0.3±0.07	0.01

Values are means (±SD). To convert serum free T_4 values to pmol/L, multiply by 12.9; and to convert serum free T_3 values to pmol/L, multiply by 15.4.

Conclusion In children with thyroid hemiagenesis the left lobe of the thyroid gland is nearly always missing, and the hemiagenesis is usually accompanied by a slight increase in TSH secretion and some compensatory enlargement of the remaining lobe.

COMMENTARY

The results of this study may be taken as indicating the frequency and characteristics of thyroid hemiagenesis in the general population. Studying children might be expected to provide a more accurate estimate of the frequency of this anomaly, because of the possibility that some acquired thyroid disease might completely destroy one side of the thyroid and spare the other. In fact, the frequency of hemiagenesis among adults is not higher. In the largest study of thyroid hemiagenesis, in which 71,500 adults suspected to have some thyroid disorder underwent ultrasonography, the abnormality was found in 16 people (1:4469; 0.02 percent) (1). In that study, the left lobe was missing in 15 patients and the right lobe in 1 patient (the isthmus was missing in 11 patients).

Thyroid hemiagenesis is a form of thyroid dysgenesis, which also includes thyroid agenesis, hypoplasia, and ectopy. Hemiagenesis seems to be slightly more common than thyroid dysgenesis of sufficient severity to cause congenital hypothyroidism. (Thyroid dysgenesis accounts for about 80 percent of cases of congenital hypothyroidism, which occurs with a frequency of about 1 in 3000 to 1 in 5000 infants in different countries.) While hemiagenesis has rarely been identified in infants with congenital hypothyroidism (1 in 230 infants in one study [2]), it seems clear from this study that thyroid secretion is not completely normal in children with hemiagenesis. Furthermore, it has been identified as a cause of transient neonatal hypothyroidism (3).

The striking propensity for absence of the left lobe of the thyroid found in the two studies (and others, summarized in ref. 1) is unexplained. However, some thyroid asymmetry is common, and when present, the left side is usually slightly smaller than the right side. It is almost as if there are separate genes governing development of the right and left lobes of the thyroid.

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Corrections

Ghrelin secretion is decreased in hyperthyroidism (March 2003:3). The first sentence of the third paragraph, left column, should read "Serum ghrelin, insulin, leptin, and other substances were measured before and after treatment."

Some women with hyperthyroidism have polycystic ovaries (March 2003:4). The last sentence of the first paragraph, right column, should read "The mean serum SHBG concentration was higher and the mean serum free testosterone, DHEA, and cortisol concentrations were lower in the women with hyperthyroidism than in age-matched normal women (Table)."

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