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The Debate about Subclinical Hypothyroidism

In 2002, the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society convened a committee to plan for and conduct a conference to consider the problems of subclinical hypothyroidism and subclinical hyperthyroidism. This committee compiled some questions about the epidemiology, consequences, and effects of treatmentof these disorders, and then convened a Consensus Committee of 13 endocrinologists, epidemiologists, health service researchers, and others to consider the questions. This committee concluded that screening for thyroid dysfunction (among adults) was not justified, that there was little evidence that subclinical hypothyroidism had deleterious effects, and that treatment had no proven benefit other than to prevent progression to overt hypothyroidism (1). Nonetheless, the committee thought it "reasonable" to treat patients with serum thyrotropin (TSH) concentrations >10 mU/L. At the same time, the screening issue was addressed by two other groups, the U.S. Preventive Services Task Force and a committee convened by the Institute of Medicine of the National Academy of Sciences (on which I served); the charge to the latter was whether screening was indicated in the Medicare population. Both of these committees considered screening not justified (2,3), primarily because there were no proven benefits of treatment in patients identified by screening as having subclinical hypothyroidism. (I excluded subclinical hyperthyroidism from these comments because it is less common.)

Soon after the publication of the report of the Consensus Committee, the leadership of the three societies that had initiated the process (different from the leadership when the organizing committee was formed) decided that that the Consensus Committee's key recommendations were wrong. So another committee was appointed to endorse screening and treatment of all patients with subclinical hypothyroidism (4). In short, the sponsoring societies, albeit with new leadership, decided to disagree with the recommendations of the Consensus Committee they had created earlier.

The issue is not about the definition; subclinical hypothyroidism is a high serum TSH and a normal free thyroxine concentration, and symptoms—whether present or not—are not relevant. The issues are whether screening for subclinical hypothyroidism should be done among adults, and if present should it always be treated, no matter how small the elevation in serum TSH concentration.

Whatever one's views about screening, surely all can agree that any abnormality in serum TSH, however detected, should be confirmed by repeated measurement at an interval of at least a few weeks before thyroxine therapy is begun. Secondly, enthusiam for treatment should be tempered by the facts that the patient's symptoms, if any, may have little to do with their thyroid dysfunction, and that many patients who have slightly high serum TSH values (≤10 mU/L) (who will be the majority of those identified by screening) have normal values months to years later (2). Then there is the new study in which 85-year-old people with subclinical hypothyroidism fared better than those with lower serum TSH values (see p. 2).

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Smokers have high serum antithyroid antibody and thyrotropin concentrations less often and low serum thyrotropin concentrations more often than nonsmokers

Belin RM, Astor BC, Powe NR, Ladenson PW. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the Third National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2004;89:6077-86.

SUMMARY

Background Cigarette smoking has been found to have both inhibitory and stimulatory effects on thyroid function in different studies, and to be a risk factor for Graves' hyperthyroidism and especially ophthalmopathy. In this study the relationships between smoking and serum thyrotropin (TSH) and antithyroid antibody concentrations were determined in a large cohort of people in the United States.

Methods The study subjects were 16,046 people ranging in age from 12 to 90 years who had participated in the Third National Health and Nutrition Survey (NHANES III) in 1988–1994, and for whom demographic, smoke exposure, urinary iodide, and serum TSH (normal range, 0.4 to 4.6 mU/L), anti-thyroid peroxidase (anti-TPO) antibody (normal, <0.5 U/ml), and antithyroglobulin (anti-Tg) antibody (normal, <1.0 U/ml) results were available. Smoking or smoke exposure was determined by measurement of serum cotinine, a long-lived metabolite of nicotine; people with concentrations >15 ng/ml were designated active smokers, and those with concentrations ≤15 ng/ml as nonsmokers.

Results There were 5134 active smokers (32 percent) (mean age, 40 years) and 10,912 nonsmokers (68 percent) (mean age, 44 years). More men were active smokers than women, and among the smokers relatively more were white and black and fewer were of Hispanic and other race-ethnicity, as compared with nonsmokers.

As compared with nonsmokers, fewer active smokers had serum TSH concentrations >4.5 mU/L (2.6 vs. 5.4 percent [odds ratio, 0.5; 95 percent confidence interval, 0.4 to 0.6]). Other factors associated with serum TSH concentrations >4.5 mU/L were increasing age, female sex, white or Hispanic race-ethnicity and higher urinary iodide excretion. Adjustment for these had little effect on the prevalence of serum TSH concentrations >4.5 mU/L (active smokers, 3.4 percent; nonsmokers, 5.4 percent).

Serum TSH concentrations were <0.1 mU/L in 0.6 percent of active smokers and 0.3 percent of nonsmokers (odds ratio, 0.5; 95 percent confidence interval, 0.2 to 1.2), and the concentrations were 0.1 to 0.4 mU/L in 2.2 and 1.2 percent, respectively (odds ratio, 2.0; 95 percent confidence interval, 1.3 to 2.9).

As compared with nonsmokers, fewer active smokers had high serum antithyroid antibody concentrations (either antibody, or both) (11 vs. 18 percent [odds ratio, 0.6; 95 percent confidence interval, 0.5 to 0.7]). Other factors associated with a high serum antithyroid antibody concentration were age, female sex, white or Hispanic race-ethnicity, and higher urinary iodide excretion. Adjustment for these factors had little effect on the prevalence of high concentrations (active smokers, 13 percent; nonsmokers, 18 percent).

Among subjects with high serum antithyroid antibody concentrations, the likelihood of a high serum TSH concentration was lower in active smokers than in nonsmokers (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 0.97).

Conclusion Among smokers, serum TSH concentrations are low more often and serum TSH and antithyroid antibody concentrations are high less often than in nonsmokers.

COMMENTARY

The one component of cigarette smoke that is known to alter thyroid function is thiocyanate, which inhibits thyroid iodide transport. This cannot be important, because there are more studies indicating that smoking augments thyroid function that there are studies indicating that it inhibits thyroid function. Nowhere has this been demonstrated better than in this large study in which, as compared with nonsmokers, fewer active smokers had high serum TSH concentrations and more had low concentrations. The lower serum TSH concentrations are likely caused by small, TSH-independent increases in thyroid secretion, as documented in other studies by a higher frequency of thyroid enlargement and slightly higher serum thyroid hormone and thyroglobulin concentrations in smokers than nonsmokers (1,2). In short, smoking is more likely to induce thyroid autonomy than thyroid deficiency.

What about the effects of smoking on thyroid autoimmune disease? The lower frequency of high serum antithyroid antibody concentrations in active smokers suggests that they have a lower frequency of autoimmune thyroiditis, and fits with their lower frequency of high serum TSH concentrations. It does not fit with the well-documented increase in Graves' hyperthyroidism in smokers (1), although the effects of smoking to cause mild thyroid autonomy with low serum TSH concentrations might somehow predispose to Graves' hyperthyroidism in smokers (1).

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Low thyroid function is not associated with decreased performance or cognitive function or increased mortality in old age

Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. JAMA 2004;292:2591-9.

SUMMARY

Background The frequency of thyroid dysfunction, particularly subclinical thyroid dysfunction, increases with age, but the clinical consequences are uncertain. In this study thyroid function was assessed in a cohort of 85-year-old subjects who were then followed for four years with annual studies of disability, depression, and cognitive function.

Methods The study subjects were all consenting 85-year-old residents of Leiden, the Netherlands, in 1997–1999. Thyroid function was assessed at base line and age 88 years. Activities of daily living (ADLs) (personal care), instrumental ADLs (housework activities), cognitive function (Mini-Mental State Examination [MMSE]), tests of attention, cognitive speed, and memory in those with high MMSE scores), and depressive symptoms (Geriatric Depression Scale), were assessed yearly for four years.

Results At base line, there were 558 subjects (369 women [66 percent] and 189 men [34 percent]). Among them, 455 (82 percent) were living independently, 458 (82 percent) were independent in ADLs, 218 (39 percent) were independent in instrumental ADLs, 386 (69 percent) had good cognitive function, and 358 (77 percent) had no severe depressive symptoms. Plasma thyrotropin (TSH) and free thyroxine (T_4) concentrations were normal in 472 subjects (85 percent); 30 (5 percent) had subclinical hypothyroidism, 37 (7 percent) had overt hypothyroidism, 17 (3 percent) had subclinical hyperthyroidism, and 2 (0.4 percent) had overt hyperthyroidism. The 39 patients with overt thyroid dysfunction were referred to their physicians, but according to pharmacy records none was treated with T_4 or an antithyroid drug.

There was no correlation between plasma TSH or free T_4 concentrations and any of the performance measures or depressive symptoms at base line. All performance measures decreased and depressive symptoms increased during follow-up. Higher base-line plasma TSH concentrations were not associated with a more rapid decrease in any measure during follow-up, and were associated with less of a decrease in performance of instrumental ADLs. Higher base-line plasma free T_4 concentrations were not associated with a more rapid decrease in any performance measure during follow-up.

During follow-up, 209 subjects (37 percent) died. Higher plasma TSH and lower plasma free T_4 concentrations at base line were associated with lower all-cause mortality (Table), cardiovascular mortality, and noncardiovascular mortality, and in both women and men.

Table. All-Cause Mortality Risk in 85- to 89-Year-Old Subjects per SD Increase in Base-Line Plasma TSH and Free T_4 Concentrations.

	Hazard Ratio*	P Value
Plasma TSH (SD, 2.7 mU/L)	0.77 (0.63-0.94)	0.009
Plasma free T_4 (SD, 0.21 ng/dl [2.7 pmol/L])	1.16 (1.04-1.30)	0.009

*Mean (95 percent confidence interval), adjusted for base-line health status, no. of chronic illnesses, and MMSE score.

At age 88 years, plasma TSH and free T_4 values were normal in 296 subjects who had normal base-line values. Among the 21 subjects with subclinical hypothyroidism studied again, 8 had subclinical hypothyroidism, 11 were normal, and 2 had overt hyperthyroidism. Among the 12 subjects with subclinical hyperthyroidism studied again, 1 had overt hyperthyroidism, 5 had subclinical hyperthyroidism, 5 were normal, and 1 had overt hypothyroidism.

Conclusion Among older subjects followed for four years, neither high plasma TSH nor low plasma T_4 concentrations are associated with deterioration of ability to perform activities of daily life, cognitive function, or depression.

COMMENTARY

These results indicate that neither hypothyroidism nor hyperthyroidism has deleterious effects on the performance of activities of daily living, cognitive function, and mood in 85-year-old subjects. Higher base-line plasma TSH values, and lower plasma free T_4 values, were associated with lower mortality, and lower plasma TSH values with less of a decrease in performance of some ADL. The testing was comprehensive, and the follow-up was nearly complete.

One might expect a thyroid-disease mortality curve to be U-shaped, with higher mortality at both ends. Might these subjects, having lived 85 years, had some characteristics that negated the deleterious effects of hypothyroidism, thereby abolishing one arm of the U? Possibly, but what might those characteristics be? Another possibility is that those at risk for death from hypothyroidism had already died, but the frequency of subclinical and overt hypothyroidism (12 percent) was similar to that found in other surveys.

These results provide no support for screening for or treating subclinical hypothyroidism in older people, but the situation with respect to hyperthyroidism may be different. Even though not associated with any disabilities at base line or thereafter, it was associated with an increase in mortality. And unlike hypothyroidism, hyperthyroidism, including subclinical hyperthyroidism, is associated with problems that can lead to fatal outcomes, namely atrial fibrillation and osteoporosis.

Robert D. Utiger, M.D.

Quality of life is decreased in patients with hyperthyroidism caused by Graves' disease

Elberling TV, Rasmussen AK, Feldt-Rasmussen U, Hording M, Perrild H, Waldemar G. Impaired health-related quality of life in Graves' disease: a prospective study. Eur J Endocrinol 2004;151:549-55.

SUMMARY

Background Patients with hyperthyroidism have many somatic and psychologic symptoms, but how much do these symptoms affect the patients' quality of life? In this study, quality of life was assessed in patients with hyperthyroidism caused by Graves' disease before and after treatment. Psychologic symptoms also were assessed before treatment to determine their impact on quality of life at that time.

Methods The study was done in 30 patients (29 women, 1 man; mean [±SD] age, 36±10 years) with newly diagnosed Graves' hyperthyroidism and 34 normal subjects (30 women, 4 men; mean age, 36±11 years). The 30 patients were among 53 patients consecutively referred to an endocrine department, the others being excluded because of psychiatric and other disorders. The diagnosis of Graves' hyperthyroidism was based on biochemical findings of overt hyperthyroidism, a high serum concentration of thyrotropin (TSH)-receptor antibodies, and diffuse thyroid radionuclide uptake. Nine patients (30 percent) had ophthalmopathy, mild in all but one.

At the time of diagnosis, quality of life was assessed using the Short-Form Health Status Survey (SF-36), a 36-item questionnaire in which the responses are subdivided into eight subscores (Table), each scored from 0 to 100 (0, poor health; 100, better health). The 17-item Hamilton Depression Rating Scale, the 14-item Hamilton Anxiety Scale, and the 11-item Bech-Rafaelsen Mania Scale were also administered then. The patients were treated with methimazole, and the SF-36 was administered again when they were euthyroid (mean, 4 months) and one year later.

Results At diagnosis, the patients' scores on the subscores of the SF-36 were lower that those of the normal subjects, except for bodily pain (Table), and they had higher depression and anxiety scores. Patients with higher depression and anxiety scores had lower scores for physical functioning, physical role limitations, general health, social functioning, and emotional role limitations. There was no correlation between any SF-35 scores and serum thyroxine or triiodothyronine concentrations.

Table. Median SF-36 and Other Scores in Normal Subjects and Patients with Graves' Hyperthyroidism before and during Antithyroid Drug Therapy.

	Normal Subjects	Patients with Hyperthyroidism		
		At Diagnosis	Euthyroid	One Year
SF-36				
Physical functioning	100	70*	95	100
Physical role limitations	100	50*	100	100
Bodily pain	92	82	100	100
General health perception	87	75*	77*	82
Vitality	80	43*	70	80
Social functioning	100	88*	100	100
Emotional role limitations	100	67*	100	100
Mental health	88	66*	80	84
Depression rating scale	0	8*		
Anxiety rating scale	0	11*		
Mania scale	0	2		

* P<0.01, as compared with the normal subjects.

By the time they were euthyroid, most patients had normal or nearly normal scores, and there was further improvement at one year. The improvement was not as marked when the scores for the eight subscales were grouped into a physical component score and a mental component scale; the respective scores were ≥2 SD below the normal mean in 63 and 43 percent of the patients at diagnosis and 14 and 11 percent at one year. The patients with ophthalmopathy differed only in that they had a slightly lower score for general health perception than those with no ophthalmopathy.

Conclusion Patients with Graves' hyperthyroidism have a decrease in health-related quality of life that is reversed by treatment.

COMMENTARY

The SF-36 is widely used to assess the effects of illness on how people feel and function both physically and mentally, more or less independently of the particular symptoms and signs of that illness, and the responses are considered a valid indication of the overall effects of the illness. In these patients with hyperthyroidism quality of life clearly was decreased, and it improved substantially in four months. They had mild to moderately severe biochemical hyperthyroidism [mean serum free thyroxine, 3.5 ng/dl [45.6 pmol/L]), but its severity did not correlate with any of the SF-36 scores, just as it does not correlate well with the frequency or severity of the usual symptoms and signs of hyperthyroidism.

How do these symptoms and signs relate to changes in quality of life, as assessed by the SF-36? For example, what is more important—tremor, anxiety, or palpitations? What about the ability to eat more but not gain weight, which some patients view as improving their quality of life? Unfortunately, nothing is said about symptoms or signs of hyperthyroidism, but it would be interesting to relate them to the nonspecific measures of quality of life, and the results just might help in selecting therapy.

Robert D. Utiger, M.D.

Agranulocytosis may be more common in propythiouracil- than carbimazole-treated patients

Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. Clin Endocrinol (Oxf) 2004;61:589-94.

SUMMARY

Background There are three widely used antithyroid drugs—carbimazole, methimazole, and propylthiouracil. Carbimazole itself is inactive, but it is rapidly converted to methimazole, and its effects are probably due to the latter. The most serious adverse effects of these drugs are hematologic and hepatic, but data concerning their frequency are sparse. This study determined the frequency of adverse effects of the drugs based on spontaneous reporting.

Methods Since 1963, physicians and other health personnel in the United Kingdom have been asked to report adverse drug effects, with supporting information, to the Committee on Safety of Medicines. More complete information was sought starting in 1991. All reports of adverse effects of carbimazole (methimazole is not available there) and propylthiouracil from 1963 to 2003 were reviewed. The number of prescriptions for each drug dispensed from 1981 to 2003 was obtained from the Department of Health.

Results During the 40-year study period, there were 725 reports of serious adverse effects for carbimazole, of which 42 (6 percent) were fatal, and 84 reports for propylthiouracil, of which 3 (4 percent) were fatal (Table 1).

From 1991 to 2003, when more detailed information was available, there were 54 reports of agranulocytosis (Table 2), and 63 reports of neutropenia (carbimazole, 51; propylthiouracil, 12), with a total of 6 deaths. The characteristics of the patients with neutropenia were similar to those for agranulocytosis shown in Table 2.

Table 1. Serious Adverse Effects of Carbimazole and Propylthiouracil (1963–2003).

	Carbimazole		Propylthiouracil	
	Total	Fatal (%)	Total	Fatal (%)
Agranulocytosis*	94	18 (19)	12	1 (8)
Neutropenia*	85	2 (2)	14	1 (7)
Aplastic anemia	10	5 (50)	0	0
Thrombocytopenia	17	3 (18)	1	0
Pancytopenia	7	1 (14)	1	0
Hepatitis	65	2 (3)	6	0
Vasculitis	2	0	7	1 (14)
Birth defects	59	3 (5)	7	0
Other		8		0

*Exact cell counts rarely reported, but probably $<0.5\times10^9$cells/L for agranulocytosis and $<2.0\times10^9$ for neutropenia, based on standard practice.

Table 2. Clinical and Treatment Characteristics of 54 Patients with Carbimazole- or Propylthiouracil-Related Agranulocytosis.

	Carbimazole (n=45)	Propylthiouracil (n=9)
Sex (F: M)	39:6	8:1
Median age (range)	51 (18-86)	50 (22-78)
Median (range) dose (mg/day)	40 (10-80)	300 (50-1200)
Median (range) days of therapy	31 (14-105)	33 (17-75)

Based on 5.23 million prescriptions dispensed (1981-2003), of which 94 percent were for carbimazole, the rate of all adverse effects per million prescriptions was 98 for carbimazole and 240 for propylthiouracil. The respective rates for specific adverse effects were 13 and 38 for agranulocytosis, 16 and 42 for neutropenia, 10 and 22 for rash, and 15 and 22 for hepatobiliary disorders.

Conclusion Based on spontaneous reporting of adverse effects, agranulocytosis is the most common life-threatening adverse effect of carbimazole and propylthiouracil, and on a per prescription dispensed basis it and other adverse effects are more common in patients treated with the latter.

COMMENTARY

Since the mid-1950s there has been debate about the relative toxicity of the three antithyroid drugs. In the most extensive experience, of over 30,000 patients with Graves' hyperthyroidism, the frequency of agranulocytosis was 0.4 percent (16 of 4373) in patients treated with propylthiouracil and 0.4 percent (93 of 26,425) of patients treated with methimazole (1). The results of this new study differ, but are consistent with older reviews indicating a higher rate in patients treated with propylthiouracil (for example, 2). However, the new data were based exclusively on spontaneous reporting, which could be subject to biases. For example, propylthiouracil is prescribed much less often in the United Kingdom than elsewhere, and many prescribing physicians may have been unfamiliar with its adverse effects, and hence more likely to report them. Also, it may have been given to patients who previously had an adverse reaction to carbimazole, a group possibly more susceptible to adverse effects of propylthiouracil.

If, as suggested by these new data, there is a difference in the frequency of agranulocytosis, it is likely to be most evident if the dose of methimazole or carbimazole is low, since major adverse effects have rarely been reported in patients given ≤15 mg daily (3).

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Octreotide is not an effective therapy for patients with Graves' ophthalmopathy

Dickinson AJ, Vaidya B, Miller M, Coulthard A, Perros P, Baister E, Andrews CD, Hesse L, Heverhagen JT, Heufelder AE, Kendall-Taylor P. Double-blind, placebo-controlled trial of octreotide long-acting repeatable (LAR) in thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 2004;89:5910-5.

SUMMARY

Background Graves' ophthalmopathy is characterized by lymphocytic infiltration and inflammation of orbital fibroadipose tissue. These cells may secrete or have receptors for signaling molecules, including somatostatin. This study evaluated the efficacy of the somatostatin receptor antagonist octreotide in patients with ophthalmopathy.

Methods The study was a randomized, double-blind study of long-acting octreotide (octreotide-LAR) and placebo in 50 patients (39 women, 11 men; mean age, 50 years) with active Graves' ophthalmopathy, as defined by the presence of periorbital and orbital inflammation (Clinical Activity Score ≥3, of a possible 7 points). All patients had normal thyroid function and stable or increasing ophthalmopathy for two months before the study started.

The patients were randomly assigned to receive 30 mg of octreotide-LAR or placebo given intramuscularly every four weeks for 16 weeks. All then received octreotide-LAR for 16 weeks, and finally all were followed without therapy for 24 weeks. The Clinical Activity score, an Ophthalmopathy Index, which includes assessment of soft-tissue inflammation, proptosis, intraocular pressure, and diplopia (possible score, 0 to 14), and a Soft Tissue Inflammation score (possible score, 0 to 5), were determined, and symptom and ophthalmopathy quality-of-life questionnaires were completed at base line and at 16, 32, 44, and 56 weeks. Four-hour orbital indium-111 (In-111)-pentetriotide uptake was measured and magnetic resonance imaging of the orbits was done at base line and at 16 and 32 weeks.

Results At base line, the age, sex, smoking status, severity and duration of ophthalmopathy, and previous therapy were similar in both groups. The mean Clinical Activity scores in the octreotide-LAR and placebo groups were 5.4 and 5.8, respectively, and the Ophthalmopathy Index scores were 7.2 and 6.4 and the Soft Tissue Inflammation scores were 1.6 and 1.7, respectively.

During the octreotide-LAR–placebo phase, the Ophthalmopathy Index decreased slightly in both groups, with a slightly greater fall in the octreotide-LAR group (−1.1 vs. –0.2). The score decreased by ≥2 points in eight patients in the octreotide-LAR group and four patients in the placebo group (but increased by ≥2 points during weeks 16 to 32 in three patients in the octreotide-LAR group and one patient in the placebo group). The Clinical Activity and Soft Tissue Inflammation scores decreased slightly in both groups, and the patients in both groups reported decreases in symptoms and increases in quality of life, but there were no differences between the groups.

During weeks 16 to 32, when both groups received octreotide-LAR, there was little change in any measure of ophthalmopathy. During weeks 32 to 56, when no treatment was given, all three scores declined slightly in both groups. Overall, the scores had decreased to the same extent from base line in both groups (the final Clinical Activity scores were approximately 2.8 in both groups). The patients in both groups continued to report improvement throughout the study, but there were no differences between the groups.

The orbital uptake of In-111-pentetreotide was increased in one or both eyes at base line in 64 percent of the patients, but there was no correlation between the uptake at base line and changes during treatment. Eye-muscle volume, as assessed by magnetic resonance imaging, decreased slightly in both groups at 32 weeks.

Conclusion Treatment with octreotide-LAR for 16 weeks is no more effective than placebo in patients with moderately severe Graves' ophthalmopathy.

COMMENTARY

Somatostatin receptors are present on many cells, including lymphocytes, and many tissues, including retroorbital tissue, and uptake of radiolabeled somatostatin analogs is often increased at sites of inflammation, including in retroorbital tissue of patients with Graves' ophthalmopathy. There are five types of somatostatin receptors (SST1-5), and most if not all, especially types 2 and 5, have been found in lymphocytes and orbital fibroblasts of patients with Graves' ophthalmopathy and, to a lesser extent, normal subjects (1). The finding that retroorbital uptake of radiolabeled somatostatin analogs is increased in these patients provides in vivo evidence of increased receptors.

If the receptors are there, they must be doing something. So, why not activate them with somatostatin or longer-acting analogs, especially considering that conventional treatment for ophthalmopathy is not very satisfactory? There were hints of benefit of somatostatin analogs in several uncontrolled studies, but the benefit might simply have reflected the natural tendency of Graves' ophthalmopathy to stabilize and gradually regress. The results of this trial support the latter interpretation.

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Hypothyroidism is rare among patients requiring prolonged mechanical ventilation

Datta D, Scalise P. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. Chest 2004;126:1307-12.

SUMMARY

Background Patients with hypothyroidism may have respiratory problems as a result of upper airway obstruction, respiratory-muscle weakness, alveolar hypoventilation, decreased hypoxic or hypercapneic ventilatory drive, or pleural effusion. Hypothyroidism could, therefore, contribute to ventilatory dependency in patients with severe lung disease. In this retrospective case study the frequency of hypothyroidism was determined in patients with respiratory failure admitted to a regional center for weaning from mechanical ventilation.

Methods Between 1999 and 2002, serum thyrotropin (TSH) was measured in 140 of 173 patients (81 percent) with respiratory failure at the time of admission to the regional weaning center. All the patients had required mechanical ventilation for at least three weeks. There were 73 women (52 percent) and 67 men (48 percent), with a mean (±SD) age of 66±15 years. The causes of respiratory failure were chronic obstructive ling disease in 39 patients (28 percent), cardiovascular surgery in 39 (28 percent), noncardiovascular surgery in 21 (15 percent), pneumonia in 21 (15 percent), and neuromuscular disease in 20 (14 percent). The patients' records were reviewed for a history or the presence of thyroid disease, clinical manifestations of thyroid disease, causes of respiratory failure, and success of weaning, defined as no requirement for ventilatory support for at least a week.

Results Among the 140 patients, the serum TSH concentrations ranged from 0.19 to 121.0 mU/L. Seventeen patients (12 percent) had high serum TSH concentrations, including 1 patient with a history of hypothyroidism who was receiving thyroid hormone therapy. The serum TSH concentrations in these 17 patients ranged from 5.5 to 121.0 mU/L; the values ranged from 5.5 to 8.0 mU/L in 9 patients and from 11.5 to 121.0 mU/L in the other 8 patients. Two of these 8 patients and 1 other patient were suspected of having hypothyroidism on clinical grounds.

Serum thyroxine (T_4) was measured in 10 patients. Two patients with serum TSH concentrations ≤8.0 mU/L had normal values, and the 8 patients with serum TSH values >8.0 mU/L had values ranging from 0.9 to 7.1 μg/dl (11.6 to 91.6 nmol/L). Four patients (3 percent) were given a new diagnosis of hypothyroidism and were treated (their serum TSH concentrations were 11.7, 13.4, 29.6, and 121.0 mU/L). In the remainder the high serum TSH concentrations (range, 5.5 to 24.3 mU/L) were attributed to an improved clinical status at the time of transfer to the weaning center. Three of the 4 patients with hypothyroidism, and the patient with known hypothyroidism, were weaned from mechanical ventilation (mean, 20 days), and 1 died. Among the other 12 patients with high serum TSH values, 9 were weaned from mechanical ventilation, and 3 could not be weaned (2 of whom died).

Weaning was successful in 92 of the 140 patients (66 percent), including 13 of the 17 patients with high serum TSH concentrations (76 percent). The mean (±SD) serum TSH concentrations in the weaned and not weaned groups were, respectively, 4.2±13.0 and 4.0±4.7 mU/L (P=0.25).

Conclusion Occasional patients requiring prolonged mechanical ventilation have hypothyroidism, and when it is present appropriate therapy may facilitate weaning.

COMMENTARY

Given the multiple ways in which hypothyroidism can affect respiratory function, it is easy to conclude that it could contribute to respiratory failure and also make weaning from prolonged mechanical ventilation more difficult. However, in this study the success of weaning was comparable in the few patients with overt hypothyroidism, the slightly greater number with high serum TSH concentrations thought not to have hypothyroidism, and the cohort as a whole. This is not surprising, given the many causes of respiratory failure and the probable variations in treatment.

No one would hesitate to treat patients with overt hypothyroidism, but what about the other 12 patients with high serum TSH concentrations? The high values were attributed to recovery from critical illness. During critical illness, TSH secretion may be depressed, and not increase appropriately in response to low serum T_4 concentrations. With recovery, sensitivity to low serum T_4 concentrations returns, and serum TSH concentrations may rise to above normal (occasionally as high as 25 mU/L) for a few days. The resulting thyroid stimulation raises serum T_4 concentrations, after which serum TSH concentrations return to normal. Sometimes it is not so obvious that the patient is recovering. This transient hypothyroidism may be overt or subclinical; what distinguishes it is the setting of illness and the fact that it is transient. This may well be the explanation for the high serum TSH values in these 12 patients, but it is hard to be sure without knowing more about the patients' illnesses, treatment, and course, and, most important, the results of measurements of serum TSH and T_4 a few days later.

Robert D. Utiger, M.D.

Lean body mass is a more important determinant of thyroxine dose than fat mass, age, or sex

Santini F, Pinchera A, Marsili A, Ceccarini G, Castagna MG, Valeriano R, Giannetti M, Taddei D, Centoni R, Scartabelli G, Rago T, Mammoli C, Elisei R, Vitti P. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. J Clin Endocrinol Metab 2005;90:124-7.

SUMMARY

Background Thyroxine (T_4) is widely prescribed, either to treat patients with hypothyroidism or to overtreat patients with thyroid carcinoma. Multiple factors alter the efficacy of T_4 therapy by altering the bioavailability or clearance of T_4. They include weight and ingestion with some foods or medications. In this study the effect of variations in body composition on dosage of T_4 was determined in patients with thyroid carcinoma.

Methods Serum thyrotropin (TSH), free T_4, and free triiodothyronine (T_3) were measured in 75 patients (52 women, 23 men) with thyroid carcinoma who had been treated with the same dose of T_4 for at least six months. They were selected so that there were 25 patients in each of three body-mass-index (BMI, in kg/m^2) groups: normal weight, BMI 18.5 to 24.9; overweight, BMI 25 to 29.9; and obese, BMI ≥30. All had been treated with thyroidectomy and iodine-131, and all had undetectable basal and TSH-stimulated serum thyroglobulin concentrations. Their serum TSH concentrations ranged from 0.005 to 0.3 mU/L, and all had normal serum free T_4 and free T_3 concentrations. Total and peripheral lean and adipose tissue mass were measured by dual-photon absorptiometry.

Results The doses of T_4, expressed as either the total daily dose or μg/kg/day, were higher in the overweight and obese groups than in the normal-weight group, but the serum TSH, free T_4, and free T_3 concentrations in the three groups were similar (Table).

Table. Characteristics, Doses of T_4, and Serum TSH and Thyroid Hormone Values in the Normal-Weight, Overweight, and Obese Patients (25 Patients per Group).

	Normal-Weight	Overweight	Obese
Age (yr)	39±11	43±12	49±10
Weight (kg)	61±8	78±10	93±14
BMI (kg/m^2)	22±2	28±2	34±3
Dose of T_4 (μg/day)	128±21	139±24	151±29
Dose of T_4 (μg/kg/day)	2.1±0.3	1.8±0.3	1.6±0.2
Serum TSH (mU/L)	0.07±0.06	0.09±0.09	0.07±0.06
Serum free T_4 (ng/dl)*	1.4±0.2	1.3±0.2	1.4±0.2
Serum free T_3 (ng/dl)*	0.37±0.04	0.39±0.03	0.38±0.05

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

The daily dose of T_4 was higher in the men than in the women (160±29 vs. 130±20 μg/day), but not different when corrected for weight (1.8±0.1 vs. 1.9±0.1 μg/kg/day). The dose of T_4 was correlated with body weight ($r = 0.61$, $P<0.01$), more so with lean body mass ($r = 0.68$, $P<0.01$), and less with fat mass ($r = 0.26$, $P = 0.02$). T_4 dose and peripheral lean mass were highly correlated ($r = 0.68$, $P<0.01$), but there was no correlation with peripheral fat mass. Age and daily dose of T_4 were negatively correlated, but not after correction for lean body mass.

Conclusion The daily dose of T_4 needed to cause subclinical hyperthyroidism in patients with thyroid carcinoma is determined more by lean body mass, especially peripheral lean body mass, than body weight, fat mass, age, or sex.

COMMENTARY

These patients had no thyroid tissue, so all of the T_4 in their serum had to come from the single daily dose of T_4. Assuming that gastrointestinal absorption of T_4 is independent of weight, then their serum free T_4 concentrations are determined by the volume of distribution and rate of clearance of T_4, including its deiodinative clearance to T_3 and reverse T_3. The deiodinases catalyzing these conversions are prominently located in muscle and skin, respectively, which fits with the correlation between the dose of T_4 and lean body mass found in this study.

There is no reason to doubt that these findings are applicable to patients with spontaneously occurring hypothyroidism. However, the matter of dosage is more complicated in them, because many have some endogenous thyroid secretion, and therefore giving T_4 means that some endogenous T_4 is taken away. How much will vary, and therefore the dose required to restore euthyroidism and lower the serum TSH concentration to the same extent would tend to be less, but vary more, independent of the patient's BMI or lean body mass.

More important, the goals of therapy are different in patients with thyroid carcinoma and hypothyroidism and those with hypothyroidism alone. In the former, the goal is subclinical hyperthyroidism, whereas in the latter it is amelioration of symptoms and restoration of normal serum TSH concentrations. Many hypothyroid patients so treated do not feel well, and adding a little T_3 doesn't help. Would they feel better if given sufficient T_4 to lower their serum TSH concentrations to or just below the lower limit of normal? There is a suggestion that they would (1), but the possibility should be studied in more detail.

Robert D. Utiger, M.D.

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Triiodothyronine does not increase the efficacy of paroxetine in patients with depression

Appelhof BC, Brouwer JP, van Dyck R, Fliers E, Hoogendijk WJ, Huyser J, Schene AH, Tijssen JG, Wiersinga WM. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. J Clin Endocrinol Metab 2004:89:6271-6.

SUMMARY

Background Triiodothyronine (T_3) can accelerate the response to tricyclic antidepressant drug therapy, and it also can augment the response when it is suboptimal. This study was done to determine if the combination of a selective serotonin reuptake inhibitor and T_3 was more effective than the inhibitor alone in patients with depression.

Methods The study group consisted of 113 patients (70 women, 43 men; mean [±SD] age, 46±11 years) with a major depressive disorder who had a score of ≥16 on the Hamilton Rating Scale for Depression and normal serum free thyroxine (T_4) concentrations. They were randomly assigned to receive paroxetine plus 25 μg of T_3, paroxetine plus 50 μg of T_3, or paroxetine plus placebo daily for 8 weeks in a ratio of 1:1:2. The dose of paroxetine was 10 mg daily for 1 week, 20 mg daily for 1 week, and then 30 mg daily. Neither the patients nor the investigators were aware of treatment-group assignment. The patients were evaluated at base line and after 1, 2, 4, 6, and 8 weeks using the 17-item Hamilton Rating Scale for Depression, other rating scales for depression and anxiety, and 11 adverse effects. The primary end point was the patient's score on the Hamilton Rating Scale for Depression at 8 weeks (a response was defined as a ≥50 percent reduction in score, and remission as a score of ≤8). Serum free T_4 was measured at regular intervals.

Results The base-line demographic, psychiatric, and biochemical characteristics of the three treatment groups were similar. The major depressive disorder was mild in 17 (15 percent), moderate in 76 (67 percent), and severe in 20 (18 percent). Seven patients withdrew from the study before treatment, leaving 106 for the analysis of efficacy. Eight of these 106 patients, evenly distributed in the three groups, did not complete the study.

There was a significant decrease in the score for the Hamilton Rating Scale for Depression in each group during the 8-week study period (Table 1). The decreases in score and the proportions of patients who responded or had a remission were similar in all three groups, as was the rate of decrease in score.

Table. Scores on the Hamilton Rating Scale for Depression during Paroxetine and T_3 or Placebo Therapy in Patients with Major Depression.

Hamilton Score	25 μg T_3	50 μg T_3	Placebo	P Value
Base line	21.0	21.0	20.8	
End	11.2	13.0	11.5	
Difference	-9.8	-8.3	-9.4	0.66
Response (no.)	13 (46%)	13 (46%)	23 (46%)	0.99
Remission (no.)	9 (32%)	9 (32%)	18 (36%)	0.92

There were similar decreases in the scores for the Montgomery Asberg Depression Rating Scale, the Beck Depression Inventory, and the Hamilton Rating Scale for Anxiety, and among the women and men.

During the study, the frequency of palpitations, sweating, and nervousness was higher in the two T_3-treatment groups, especially the 50-μg T_3 group, as compared with the placebo group. There were no differences in tremor, nausea, headache, somnolence, insomnia, dry mouth, loss of libido, or erectile dysfunction. There was a dose-dependent fall in serum free T_4 concentrations, indicative of decreased thyrotropin secretion, in the T_3-treatment groups.

Conclusion In patients with depression, the combination of T_3 and paroxetine does not increase the extent or rate of response to paroxetine, and it has more adverse effects, as compared with paroxetine alone.

COMMENTARY

In this study, the first randomized trial of T_3 plus a selective serotonin reuptake inhibitor in patients with major depression, there was no hint of any benefit from the addition of T_3 to paroxetine, in terms of either increasing or accelerating the action of paroxetine. In contrast, most individual trials and meta-analyses found that addition of T_3, usually in a dose of 25 μg daily, to a tricyclic antidepressant drug was modestly beneficial, but all the studies were small and none lasted more than 35 days (1,2). The different results may relate to differences in patients and other study details, or in fundamental differences between tricyclic antidepressant drugs and selective serotonin-reuptake-inhibiting drugs. The former have both catecholaminergic and serotonergic properties. In contrast, the latter have only serotonergic properties, and they have for the most part superseded tricyclic antidepressant drugs for the treatment of depression. It is to be hoped that this new study will come to the attention of those who often prescribe antidepressant drugs and who may have assumed that addition of T_3 is beneficial in patients being treated with any antidepressant drug.

Robert D. Utiger, M.D.

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Thyroid carcinomas are more likely to contain sonographic calcifications than benign thyroid nodules

Seiberling KA, Dutra JC, Grant T, Bajramovic S. Role of intrathyroidal calcifications detected on ultrasound as a marker of malignancy. Laryngoscope 2004;114:1753-7.

SUMMARY

Background Ultrasonography is an excellent way to identify or confirm the presence of thyroid nodules, but its value for differentiating the few nodules that are carcinomas from the many that are benign is limited. Certain sonographic features may be more common among thyroid carcinomas than benign nodules, for example, hypoechogenicity, irregular borders, and microcalcifications. This retrospective study was done to determine the frequency of microcalcifications and other types of calcifications in benign and malignant thyroid nodules.

Methods The study subjects were 159 patients (122 women, 37 men; mean age, 46 years) with thyroid nodules who underwent thyroid ultrasonography and then surgery. The patients' clinical, biopsy, and histologic findings were recorded, and their sonograms were evaluated by a single radiologist. Calcifications were categorized as microcalcifications if they were hyperechoic punctate foci or small foci of reflections of echoes, and as macrocalcifications if there were large or coarse foci of echoes or the wall of the nodule was calcified.

Results Sixty-six of the 159 patients (42 percent) patients had a thyroid carcinoma; 63 were papillary carcinomas and 3 were follicular carcinomas. Among the remaining 93 patients, 32 had a follicular adenoma, 28 a multinodular goiter, 18 lymphocytic thyroiditis, 11 a hyperplastic nodule, and 4 a normal thyroid gland.

Calcifications were seen in the nodules of 88 patients (55 percent), more often in the carcinomas than the benign nodules (sensitivity for carcinoma, 79 percent; specificity, 61 percent) (Table 1).

Table 1. Presence of Calcification in 66 Thyroid Carcinomas and 93 Benign Nodules.

	Calcifications Present	No Calcifications
Carcinoma	52 (79%)	14 (21%)
Papillary	50	13
Follicular	2	1
Benign nodule	36 (39%)	57 (61%)
Follicular adenoma	10	22
Multinodular goiter	16	12
Lymphocytic thyroiditis	4	14
Hyperplastic nodule	4	7
Normal thyroid	2	2

Among the 88 patients with nodule calcifications, the calcifications were microcalcifications in 63 nodules (72 percent), macrocalcifications in 19 (22 percent), and mixed in 6 (6 percent). Most microcalcifications were in carcinomas (Table 2).

Table 2. Types of Calcification in Thyroid Carcinomas and Benign Nodules.

	Microcalcifications	Macrocalcifications	Both
Carcinoma	39 (62%)	9 (47%)	4 (67%)
Benign nodule	24 (38%)	10 (53%)	2 (33%)

Conclusion The majority of thyroid carcinomas contain calcifications, especially microcalcifications, as detected by ultrasonography, but so do some benign thyroid nodules.

COMMENTARY

Since the introduction of thyroid ultrasonography, investigators have sought findings that would distinguish benign from malignant thyroid nodules (1). In agreement with several other studies (2,3), Seiberling et al. found that the presence of microcalcifications within a thyroid nodule was associated with thyroid carcinoma, but the specificity and sensitivity of the finding remain uncertain. Consider this study. It was retrospective, and, more important, the study subjects must have been very highly selected, because 42 percent had thyroid carcinoma, as compared with only about 5 to 7 percent of unselected patients with thyroid nodules. The authors say they reviewed the results of thyroid biopsies, but do not say how many of the patients had biopsies. Given the 42 percent figure, most patients must have had a biopsy, and the results must have been at least suspicious for carcinoma. Therefore, we do not know the real sensitivity and, more important, specificity of microcalcifications as an indicator that a thyroid nodule is a carcinoma. Indeed, a sonographic finding of microcalcification is unlikely to be a reliable marker for thyroid carcinoma, and it cannot eliminate the need for biopsy. The only ultrasound findings that have a high enough sensitivity and specificity for carcinoma to warrant surgery in the absence of the results of biopsy are extranodular invasion and pathologic regional lymphadenopathy, both of which are rare (1).

It is unlikely that ultrasonography can be refined enough to distinguish reliably between benign and malignant nodules, thereby supplanting biopsy. The real hope for the future lies in the use of molecular biologic or other analysis of tissue to increase the specificity of ultrasound-guided biopsy.

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Fine-needle aspiration biopsy is not a sensitive test for detection of carcinoma in patients with a multinodular goiter

Rios A, Rodriguez JM, Galindo PJ, Montoya M, Tebar FJ, Sola J, Canteras M, Parrilla P. Utility of fine-needle aspiration for diagnosis of carcinoma associated with multinodular goitre. Clin Endocrinol (Oxf) 2004;61:732-7.

SUMMARY

Background Multinodular goiters are common, and in some patients one or more of the nodules are thyroid carcinomas. This study was done to determine the value of fine-needle aspiration biopsy of the dominant nodule and any other nodules clinically suspected to be carcinomas in patients with multinodular goiter.

Methods The study subjects were 432 patients with a multinodular goiter in whom the dominant nodule and 14 other nodules clinically suspected of being carcinomas were biopsied. Nondominant nodules were considered suspicious if they were hard, fixed to surrounding tissue, and had grown rapidly, and if the patient had a history of head and neck radiation. Ultrasound guidance was used in some instances. The biopsies were categorized by a single cytopathologist as benign-colloid if there were few follicular cells and abundant colloid; follicular tumor if there were many follicular cells arranged in microfollicles; Hurthle-cell (oncocytic) tumor; suggestive of carcinoma, based on the cytologic features of the cells; traumatic if there many red blood cells; and inadequate if there were few follicular cells and little colloid. All the patients then underwent thyroidectomy, their goiters were evaluated by light microscopy, and the cytologic and histologic results were compared.

Results Among the 446 biopsies (of 432 dominant nodules and 14 other suspicious nodules), 339 (76 percent) were benign-colloid, 75 (17 percent) were follicular tumors, 8 (2 percent) were Hurthle-cell tumors, 22 (5 percent) were suggestive of carcinoma; 2 (0.4 percent) were traumatic; and none was inadequate.

Forty-two patients (10 percent) had carcinoma, all in the dominant or a clinically suspicious nodule, and 19 of the patients had carcinoma in one or more other nodules. There were 36 papillary carcinomas (86 percent), 5 follicular carcinomas (12 percent), and 1 anaplastic carcinoma (2 percent).

Twenty-three of the 42 carcinomas were not detected by the biopsy (Table).

Table. Results of Fine-Needle Aspiration Biopsy and Histology in 430 Patients with Multinodular Goiter.

	Histology		
Biopsy	Carcinoma	No Carcinoma	Total
Benign-colloid	23	302	325
Follicular or Hurthle-cell tumor	12	71	83
Suggestive of carcinoma	7	15	22
Total	42	388	430

Conclusion Some patients with multinodular goiter have a thyroid carcinoma, which is usually the dominant nodule or a nodule with clinical features suggestive of carcinoma. However, fine-needle aspiration biopsy is not a sensitive test for detecting carcinoma in these patients.

COMMENTARY

Some nodules in multinodular goiters are carcinomas, but how often, and what is the best way to identify them? Overall, the frequency that a nodule in a multinodular goiter is a carcinoma is about the same as it is in a solitary nodule (1). The risk factors for carcinoma in patients with a multinodular goiter are similar to those for carcinoma in patients with a solitary nodule, and include a history of head and neck radiation, an enlarging nodule, and cervical adenopathy, but these are present in few patients.

Biopsy should be a reliable way to identify a nodule in a multinodular goiter that is a carcinoma, especially a papillary carcinoma, just as it is in a solitary nodule (2), but it was not in this study. Why is not clear. Nearly all of the carcinomas were in the dominant nodule, and all of the nodules that were carcinomas were biopsied, but few of the biopsies were suspicious for carcinoma. The categorization of the biopsies was unusual, because the description of the benign-colloid category reads like a description of what others would categorize as inadequate biopsies. (The authors did have an inadequate category, but none of the biopsies was categorized as such). However, assuming that the biopsies in the benign-colloid group contained adequate numbers of cells, that does not explain why the biopsies of 23 of the 36 papillary carcinomas were categorized as benign-colloid. Perhaps the lack of routine use of ultrasound guidance resulted in sampling errors within the goiters.

This study serves as a cautionary note in the otherwise widely held view that most papillary carcinomas can be identified by fine-needle aspiration biopsy. It should not matter whether the patient has a solitary nodule or multiple nodules, so long as the right nodules are biopsied. In that regard, it would seem most appropriate to biopsy the dominant nodule and any others that are ≥1 cm in longest dimension with ultrasound guidance, so that exactly what was biopsied is known.

Robert D. Utiger, M.D.

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Diagnostic whole-body radioiodine scans have little value before postoperative radioiodine therapy in patients with thyroid carcinoma

Salvatori M, Perotti G, Rufini V, Maussier ML, Dottorini M. Are there disadvantages in administering ^{131}I ablation therapy in patients with differentiated thyroid carcinoma without a preablative diagnostic ^{131}I whole-body scan? Clin Endocrinol (Oxf) 2004;61:704-10.

SUMMARY

Background Many patients with differentiated thyroid carcinoma are treated postoperatively with iodine-131 (I-131) to destroy any remaining normal thyroid tissue and carcinoma. A diagnostic I-131 scan may be done before this therapy to identify patients with no thyroid remnants, in whom I-131 therapy is not needed, but this scan may stun any remaining tumor, possibly reducing the efficacy of the treatment dose. In this retrospective study I-131 uptake in the neck and serum thyroglobulin (Tg) were measured before I-131 therapy, and the results compared with those of post-therapy scans.

Methods The study subjects were 875 consecutive patients (691 women, 184 men; mean age, 46 years [range, 12 to 79]) with differentiated thyroid carcinoma who were treated with I-131. Among them, 750 (86 percent) had papillary carcinoma and 125 (14 percent) had follicular carcinoma. Patients with a microcarcinoma (≤1 cm), distant metastases, or a high serum anti-Tg antibody concentration were excluded.

After total thyroidectomy and cessation of thyroid hormone therapy, when the patients' serum thyrotropin (TSH) concentrations were >30 mU/L, serum Tg and neck uptake of a 100-μCi (3.7-MBq) dose of I-131 were measured. The patients were then treated with I-131 (mean dose, 54 mCi [2000 MBq]). A whole-body scan was done 2 to 5 days later. The studies, including a diagnostic whole-body scan, were repeated 6 to 10 months later.

Results The post-I-131 therapy whole-body scans revealed thyroid remnants in 822 patients (94 percent), of whom 708 (86 percent) had only thyroid remnants, 70 (8 percent) lymph node metastases, 38 (5 percent) distant metastases, and 6 (1 percent) both lymph-node and distant metastases. These 822 patients were subdivided into three groups, according to their serum Tg and pre-therapy I-131 uptake values (Table). Serum Tg values were <1 ng/ml in 14 patients who had metastases, including 5 in whom the pre-therapy neck uptake value was <1 percent.

Table. Post-I-131 Therapy Scan Results and Pre-I-131 Therapy Serum Tg and Neck I-131 Uptake Values in Patients with Positive Post-Therapy Scans.

	No.	Thyroid Remnants	Thyroid Remnants and Metastases	Serum Tg (ng/ml)	Neck I-131 Uptake (%)
Serum Tg ≥1 ng/ml and pre-I-131 therapy uptake ≥1%	749 (91%)	649 (87%)	100 (13%)	18.5 (2-750)	3.7 (1-12)
Serum Tg <1 ng/ml and pre-I-131 therapy uptake ≥1%	43 (5%)	34 (79%)	9 (21%)	<1	3.6 (2-11.5)
Serum Tg <1 ng/ml and pre-I-131 therapy uptake <1%	30 (4%)	25 (83%)	5 (17%)	<1	0.5 (<1)

The post-I-131 therapy scan was negative in 53 patients (6 percent), all of whom had serum Tg values <1 ng/ml and pre-I-131 therapy neck uptake values <1 percent.

I-131 therapy resulted in thyroid ablation in 675 of the 792 patients (85 percent) who had pre-I-131 therapy neck uptake values ≥1 percent.

Conclusion Most patients with thyroid carcinoma treated by total thyroidectomy have thyroid remnants, and therefore routine diagnostic whole-body scanning before I-131 therapy is not necessary.

COMMENTARY

Total thyroidectomy is seldom achieved in patients with thyroid carcinoma, as determined by scans done after administration of a high dose of I-131. Is there a good way to detect thyroid remnants or metastases postoperatively before I-131 therapy is given, so that those with no remnants or metastases can be spared I-131 therapy? It can be done by measurements of neck uptake after administration of a low dose of I-131 or I-123; whole-body imaging, using a higher dose; measurement of serum Tg; or a combination of these tests. Among them, whole-body imaging is most likely to detect metastases, but it is the most cumbersome and costly, and it may result in stunning of metastases if I-131 is used, potentially reducing the likelihood of their destruction by I-131 therapy. Measurements of neck uptake obviously reveal the presence of iodide-concentrating tissue in the neck, but not whether it is inside or outside of the thyroid bed, and measurements of serum Tg reveal only that some normal or malignant thyroid tissue is present somewhere. The latter two tests may miss remnants and metastases, as in a few patients in this study.

Why do any of these tests? One reason is to identify patients who had a total thyroidectomy and have no metastases, and who therefore need not be given I-131. Another is that metastases may be detected unexpectedly, leading to administration of a higher dose of I-131 than that usually given for remnant destruction. Both of these groups are small, and among the latter the metastases might be destroyed by the usual dose. Therefore, for most patients pre-I-131 therapy studies, particularly uptake measurements or imaging, are not necessary.

Robert D. Utiger, M.D.

Patients with medullary thyroid carcinoma are more likely to have a coincidental papillary thyroid carcinoma than are patients with other thyroid disorders

Biscolla RP, Ugolini C, Sculli M, Bottici V, Castagna MG, Romei C, Cosci B, Molinaro E, Faviana P, Basolo F, Miccoli P, Pacini F, Pinchera A, Elisei R. Medullary and papillary tumors are frequently associated in the same thyroid gland without evidence of reciprocal influence in their biologic behavior. Thyroid 2004;14:946-52.

SUMMARY

Background Papillary microcarcinomas, usually defined as carcinomas ≤1 cm in longest dimension, are common, and are found in not only otherwise normal thyroid glands but also in multinodular goiters, the hyperplastic thyroid glands of patients with Graves' disease, and thyroid glands with other tumors, including medullary carcinomas. This study was done to determine the prevalence and characteristics of papillary carcinoma in patients with medullary carcinoma and other thyroid disorders.

Methods The study subjects were 196 consecutive patients (120 females, 76 males; mean age, 48 years [range, 13 to 83]) with medullary carcinoma of the thyroid seen at a single center. The histologic sections of the thyroid gland of these patients, 1657 patients with multinodular goiter, and 311 patients with hyperthyroidism caused by Graves' disease were reviewed. Serum calcitonin was measured as part of the initial evaluation of many patients. DNA from white cells or tumor was analyzed for *RET* mutations in 181 of the patients with medullary carcinoma.

Results Twenty-seven of the 196 patients (14 percent) had both a medullary carcinoma and a papillary carcinoma. Among them, the medullary carcinoma was suspected because of a high serum calcitonin value in 15, it was found at surgery for a multinodular goiter in 6 (no serum calcitonin assay before surgery), and it was found at surgery for a nodule suspected and later proven to be a papillary carcinoma in 6 (2 of whom had a high serum calcitonin value before surgery). The papillary carcinomas were microcarcinomas in all 21 patients in the first two groups, and were >1 cm in all 6 patients in the latter group. The patients were treated by thyroidectomy and lymph node disection.

The tumors were distinct in all 27 patients, and they were in different lobes of the thyroid in 21 (78 percent). All the medullary carcinomas stained with calcitonin and chromogranin antibodies, but not thyroglobulin antibodies; conversely, all the papillary carcinomas stained only with thyroglobulin antibodies. Five patients (18 percent) had a germline *RET* mutation, and in them the mutation was found in both tumors (among the 169 patients with medullary carcinoma alone 16 percent had a germline *RET* mutation).

There were no differences in the stage of the medullary carcinoma in the 27 patients with both medullary and papillary carcinomas and the 169 patients with medullary carcinoma alone at the time of diagnosis.

Incidental papillary carcinomas were found in 106 of the 1657 patients with a multinodular goiter (6 percent) and 16 of the 311 patients with Graves' hyperthyroidism (5 percent) treated by surgery.

Conclusion Some patients with medullary thyroid carcinoma also have a papillary thyroid carcinoma. The latter are distinct tumors, and their presence does not alter the outcome of the patients.

COMMENTARY

These 27 patients who had both a medullary carcinoma and a papillary carcinoma clearly had separate tumors. In 21 of them, the papillary carcinoma was an incidentaloma, and was not likely to alter the patient's course. In the other 6 patients the medullary carcinoma was the incidenaloma. The results also indicate that papillary carcinomas are more common in patients with medullary carcinoma than in those with a multinodular goiter or Graves' hyperthyroidism. In another study, 12 of 82 patients with medullary carcinoma (15 percent) had a separate papillary microcarcinoma, as compared with 498 of 7313 patients (7 percent) who underwent thyroidectomy for other reasons (1).

There is no obvious reason for the combination. Calcitonin has no known effects—paracrine or endocrine—on thyroid follicular cells, and *RET* mutations are not associated with papillary carcinoma. The answer may lie in differences in the diligence with which the operative specimens were evaluated.

The presence of separate medullary and papillary carcinomas is not to be confused with the rare mixed medullary-follicular carcinomas, in which both cell types are intermingled (2). In these tumors the two cell types do not seem to be derived from a common precursor; the medullary carcinoma cells are monoclonal, whereas the follicular cells are oligoclonal or polyclonal, and rarely are calcitonin and thyroglobulin present in the same cells.

Robert D. Utiger, M.D.

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Basal but not stimulated serum thyroglobulin values vary according to number and site of metastases in patients with thyroid carcinoma

Robbins RJ, Srivastava S, Shaha A, Ghossein R, Larson SM, Fleischer M, Tuttle RM. Factors influencing the basal and recombinant human thyrotropin-stimulated serum thyroglobulin in patients with metastatic thyroid carcinoma. J Clin Endocrinol Metab 2004;89:6016-6.

SUMMARY

Background Measurements of serum thyroglobulin (Tg), both basally and in response to increases in serum thyrotropin (TSH) concentrations, are the most sensitive test for persistent or recurrent tumor in patients with differentiated thyroid carcinoma. This retrospective study was undertaken to determine the relationships between basal and TSH-stimulated serum Tg values and tumor volume, location, and type in patients with thyroid carcinoma.

Methods The study subjects were 417 patients (258 women, 159 men) with differentiated thyroid carcinoma. All had been treated by thyroidectomy, and most had been treated with iodine-131 (I-131) for remnant ablation or metastatic tumor. All were taking thyroxine in a dose sufficient to reduce their serum TSH concentrations to <0.2 mU/L. Patients with high serum anti-Tg antibody concentrations were excluded. For each patient the histologic diagnosis was confirmed, serum Tg was measured before and after administration of two 0.9-mg doses of TSH, and a whole-body diagnostic I-131 scan was done. Patients with detectable basal or stimulated serum Tg values underwent ultrasonography of the neck and often other imaging tests. Based on these studies, the patients were categorized as having no evidence of tumor, a thyroid remnant or tumor limited to the thyroid bed, and tumor outside the thyroid bed.

Results Among the 417 patients, 201 (48 percent) had no evidence of persistent or recurrent tumor, 47 (11 percent) had a thyroid remnant or tumor in the thyroid bed, and 169 (41 percent) had metastatic tumor (bone, 38; lung, 91; mediastinum, 74; and neck, 104). The characteristics of the patients in these groups and their serum Tg values are shown in the Table.

Table. Clinical Findings and Serum Tg Values (Median and Range) in 417 Patients with Thyroid Carcinoma.

	No Evidence of Tumor (n=201)	Thyroid Remnant or Tumor in Thyroid Bed (n=47)	Metastatic Tumor (n=169)
Women/men	129/72	34/13	95/74
Age (yr)	44	50	49
TMN stage* (I/II/III/IV) (no.)	114/35/48/4	23/12/10/0	59/20/46/44
Histology			
Papillary (no.)	174	31	119
Follicular (no.)	6	5	18
Hurthle-cell (no.)	7	5	9
Poorly differentiated (no.)	3	1	12
Basal serum Tg (ng/ml)	0.6 (<0.3-7.6)	0.6 (<0.3-66)	12 (<0.3-65,400)
Stimulated serum Tg (ng/ml)	1.2 (<0.3-26)	1.2 (<0.3-250)	66 (0.6-97,400)
Times increase in serum Tg (ng/ml)	1.3 (<0.3-10)	2.0 (0.8-62)	3.3 (0.3-41)
Increment in serum Tg (ng/ml)	0.4 (0-20)	0.6 (0-246)	42 (0-42,400)

*TMN denotes tumor, node, and metastasis.

In general, patients with bone metastases had the highest basal serum Tg values, followed by those with lung, mediastinal node, and cervical node metastases. Overall, basal serum Tg values were correlated with the extent of tumor, and most patients with very high values had metastases at multiple sites. The times increase in serum Tg values after TSH stimulation also varied considerably, and correlated poorly with the volume or site of metastases.

Conclusion In patients with metastatic thyroid carcinoma, basal serum Tg concentrations are correlated with the extent and site of metastases, but the increase after exogenous TSH stimulation is not.

COMMENTARY

The results of this study address two questions relevant to the care of patients with thyroid carcinoma. One, what basal and TSH-stimulated serum Tg values indicate that the patients have no persistent or recurrent tumor, and therefore need no further evaluation? Two, if high, do the results provide information about the extent and location of the tumor? The results do identify patients who need no further evaluation. They are mostly patients with low-stage papillary carcinoma with low basal and stimulated serum Tg concentrations. Indeed, in them, serum Tg probably need not be measured after TSH stimulation (or cessation of thyroxine therapy). On the other hand, high serum basal and stimulated Tg values offer only a rough clue as to the site(s) and amount of tumor. One may start with ultrasonography of the neck if the values are not very high, or lung and bone imaging if they are very high, but most patients need multiple imaging studies, including a diagnostic whole-body I-131 (or I-123) scan. In this group of patients, serum Tg need not be measured after TSH stimulation if the basal serum Tg concentration is very high (>66 ng/ml in this study, and this one value might have been an outlier).

Given the cost of recombinant TSH and the symptoms that may occur when thyroxine therapy is stopped, serum Tg should be measured in advance of either procedure to be sure that there is something more to be learned by measuring it after exogenous or endogenous TSH stimulation.

Robert D. Utiger, M.D.

Thyroid autoimmunity is a risk factor for miscarriage

Sieiro Netto L, Medina Coeli C, Micmacher E, Mamede Da Costa S, Nazar L, Galvao D, Buescu A, Vaisman M. Influence of thyroid autoimmunity and maternal age on the risk of miscarriage. Am J Reprod Immunol 2004;52:312-6.

SUMMARY

Background Many pregnancies end in spontaneous miscarriage. Autoimmune thyroid disease, as manifested by high serum antithyroid antibody concentrations, may be a risk factor for miscarriage. This study evaluated the effects of thyroid autoimmunity, thyroid function, and maternal age on the risk of spontaneous miscarriage in a large group of women in Brazil.

Methods The study subjects were 534 women attending a prenatal clinic in Rio de Janeiro who were 5 to 12 weeks pregnant (women with overt thyroid dysfunction were excluded). Their mean (±SD) age was 24±6 years (range, 12 to 49); 39 (7 percent) were ≥35 years. Serum antithyroid peroxidase (TPO) antibodies, thyrotropin (TSH), and free thyroxine (T_4) were measured then, and the women were followed thereafter. Abortion was defined as the spontaneous ending of pregnancy before 20 weeks.

Results Among the 534 women, 29 (5 percent) had a high serum anti-TPO antibody concentration (>40 U/L). Their serum TSH concentrations, but not serum free T_4 concentrations, were higher than in the women with normal serum anti-TPO antibody concentrations (Table 1).

Thirteen women (2 percent) had a spontaneous miscarriage, the rate being higher in older women and women with high serum anti-TPO antibody or high serum TSH concentrations (Table 2). Multivariate analysis revealed that the three factors were independently associated with miscarriage.

Table 1. Serum TSH and Free T_4 Concentrations in Pregnant Women with High and Normal Serum Anti-TPO Antibody Concentrations.*

	High Serum Anti-TPO Value	Normal Serum Anti-TPO Value
Serum TSH (mU/L)		
<0.4	3 (10%)	62 (12%)
0.4-3.8	22 (76%)	431 (85%)
>3.8	4 (14%)	12 (3%)**
Serum free T_4 (ng/dl)		
<0.8	2 (7%)	15 (3%)
0.8-2.0	27 (93%)	488 (97%)

*Normal values (nonpregnant women and men): serum anti-TPO antibodies, ≤40 U/L; serum TSH, 0.4-3.8 mU/L, free T_4, 0.2-2.0 ng/dl [10-26 pmol/L]. **P=0.02, for the distribution of serum TSH values between the two groups.

Table 2. Risk of Miscarriage as a Function of Age and Serum Anti-TPO Antibody and TSH Concentrations.

	Total	Miscarriage (%)
Age (yr)		
<35	495	10 (2%)
≥35	39	3 (8%)
High serum anti-TPO antibody		
No	505	10 (2%)
Yes	29	3 (10%)
Serum TSH (mU/L)		
<0.4	65	1 (2%)
0.4-3.8	453	10 (2%)
>3.8	16	2 (12%)

Conclusion The risk of spontaneous miscarriage is increased in older women and women with high serum anti-TPO antibody and high serum TSH concentrations.

COMMENTARY

An association between serum anti-TPO and antithyroglobulin antibody concentrations and an increased risk of spontaneous miscarriage was recognized 15 years ago (1). This association was independent of thyroid hormonal status. The results of subsequent studies of thousands of women in the United States, Europe, and Asia were similar; on average the risk was increased 2- to 3-fold, but was sometimes higher (2). High serum antithyroid antibody concentrations have also been associated with recurrent miscarriage, defined as three or more spontaneous pregnancy losses.

In this new study, serum anti-TPO antibodies were measured in 534 Brazilian women in the first trimester of pregnancy. The 2 percent rate of spontaneous miscarriage before 20 weeks was considerably lower than the rate of 15 to 20 percent typically reported in the literature. The 5 percent rate of thyroid autoimmunity, defined as a high serum anti-TPO antibody concentration, was also lower than typically reported (2). This rate would have been somewhat higher had serum antithyroglobulin antibodies been measured.

Nonetheless, there was a positive association between thyroid autoimmunity and spontaneous miscarriage, even after adjusting for thyroid hormonal status and maternal age. The presence of an association, despite the low rate of miscarriage, is indicative of the robustness of the relationship, and extends the reported association between thyroid autoimmunity and miscarriage to a fourth continent. Research in this area should now focus on identifying explanations for the association, and exploring intervention strategies. The finding of fetal resorption in euthyroid mice immunized with thyroglobulin offers an intriguing model for further study, and so do preliminary data that treatment with T_4 or gamma globulin reduce the miscarriage rate in women with high serum antithyroid antibody concentrations.

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Serum antithyroid antibody concentrations may decrease after treatment for *Helicobacter pylori* infection in patients with autoimmune thyroiditis

Bertalot G, Montresor G, Tampieri M, Spasiano A, Pedroni M, Milanesi B, Favret M, Manca N, Negrini R. Decrease in thyroid autoantibodies after eradication of Helicobacter pylori infection. Clin Endocrinol (Oxf) 2004;61:649-52.

SUMMARY

Background The pathogenesis of chronic autoimmune thyroiditis is not known, but likely includes genetic and environmental factors. The latter may include *Helicobater pylori* infection of the stomach. In this study the effect of treatment of *H. pylori* infection in patients with high serum antithyroid antibody concentrations was determined.

Methods Twenty-five consecutive patients with a serum antithyroid peroxidase (TPO) antibody concentration >700 U/ml were tested for *H. pylori* infection with the C-13 urea breath test. The test was positive in 18 (72 percent). Among them, 10 randomly selected patients (all women; mean [±SD] age, 46±19 years) were invited to participate in a study in which the *H. pylori* infection was treated and serum antithyroid antibodies were measured repeatedly thereafter. Five women declined; four had no gastrointestinal symptoms and one had antibiotic allergy. The remaining five women (symptoms not stated) were treated with a standard anti-*H. pylori* regimen (amoxicillin, clarithromycin, and esomeprazole) for seven days. Serum anti-TPO antibodies (normal, ≤35 U/ml) and antithyroglobulin (Tg) antibodies (normal, ≤50 U/ml) were measured at base line and periodically for up to two years in all ten women, and serum thyrotropin (TSH)-binding inhibitory immunoglobulins (TBII) were measured in two women in the treatment group.

Results The five women who received anti-*H. pylori* therapy had a progressive decrease in serum anti-TPO antibody concentrations (Table). Serum anti-Tg antibody concentrations similarly decreased in the three women who had high base-line values. Two women (patients 3 and 4) had hyperthyroidism and high serum TBII values at base line, and the values decreased later. The C-13 urea breath test was negative in all five women after therapy.

Table. Serum Antithyroid Antibody Concentrations at Base Line and after Anti-*H. Pylori* Therapy.

Patient	Anti-TPO Antibodies (U/ml)*				Anti-Tg Antibodies (U/ml)*			
	Base Line	3-6 Months	7-12 Months	13-24 Months	Base Line	3-6 Months	7-12 Months	13-24 Months
1	4755	3640	331	45	1783	1638	1234	434
2	1521	1800	1234	434	74	120	55	40
3	966	486	219	312	73	53	20	32
4	2157	1006	682	520	35	24		
5	1456	1915	1213	724	20	20	20	25

*Multiple measurements were done in several time intervals, in which case the last value is given.

In contrast, both serum anti-TPO and anti-Tg antibody concentrations changed less in the five untreated women. For example, their serum anti-TPO antibody concentrations decreased by 27 percent (range, 0 to 56 percent), as compared with 73 percent (range, 50 to 99 percent) in the treatment group. Four of the untreated women had high serum anti-Tg concentrations, and the values changed little during follow-up.

No information about the women's thyroid function at base line or thereafter is given, except that two women in the anti-*H. pylori* treatment group had hyperthyroidism.

Conclusion Serum anti-TPO and anti-Tg antibody concentrations may decrease after antibiotic and proton-pump inhibitor therapy for *H. pylori* infection in patients with chronic autoimmune thyroiditis.

COMMENTARY

Asymptomatic chronic autoimmune thyroiditis is common, and asymptomatic infection with *H. pylori* is even more common. Therefore, the high frequency of *H. pylori* infection in patients with autoimmune thyroiditis reported in other studies might be a coincidence (1,2).

This new study provides more evidence for an association between asymptomatic *H. pylori* infection and autoimmune thyroiditis. The C-13 urea breath test is a sensitive and specific test for *H. pylori* infection, and the women had very high serum anti-TPO antibody concentrations. Therefore, the diagnosis of both conditions seems secure. What is missing is information about the women's symptoms, if any, and thyroid function. Also, selection for anti-*H. pylori* therapy was not random. Still, most untreated women had little fall in serum antithyroid antibody concentrations.

How might *H. pylori* infection cause or activate autoimmune thyroiditis in a susceptible host? Some *H. pylori* product or an anti-*H. pylori* antibody that cross-reacted with a thyroid antigen might injure the thyroid, thereby initiating autoimmune thyroiditis. Alternatively, there might be no autoimmune thyroiditis, but simply an anamnestic rise in serum antithyroid antibody concentrations during *H. pylori* infection. The association between *H. pylori* infection and autoimmune thyroiditis may be a coincidence, but the former might prove to be an important risk factor for the latter.

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Low serum triiodothyronine concentrations predict mortality in patients with heart failure

Pingitore A, Landi P, Taddei MC, Ripoli A, L'Abbate A, Iervasi G. Triiodothyronine levels for risk stratification of patients with chronic heart failure. Am J Med 2005;118:132-6.

SUMMARY

Background Low serum triiodothyronine (T_3) concentrations are the most common of the many abnormalities in pituitary–thyroid function that occur in patients with nonthyroidal illness. The prognostic value of measurements of serum T_3 in patients with chronic heart failure was determined in this study.

Methods The study subjects were 281 consecutive patients (74 women, 207 men) hospitalized for treatment of chronic heart failure caused by dilated cardiomyopathy. During the same interval, another 46 patients with heart failure were excluded because of comorbidity (sepsis, cachexia) or overt thyroid dysfunction. All the patients had been treated for heart failure for at least one month; they were hospitalized because of increasing symptoms or decreasing cardiac function. All had an ejection fraction <45 percent and a left ventricular end-diastolic volume >56 mm. The cause of the heart failure was nonischemic dilated cardiomyopathy in 128 patients (46 percent) and postischemic dilated cardiomyopathy in 153 (54 percent), based on a history of myocardial infarction and the presence or absence of coronary artery disease as determined by angiography. Serum total and free T_3, total and free thyroxine (T_4), and thyrotropin (TSH) were measured and echocardiography was done on the second to fifth hospital days.

The mean (±SD) duration of follow-up was 12±7 months. Follow-up information was obtained from the patient's records, telephone interviews, and death certificates. Cardiac death was defined as death caused by a cardiac arrhythmia, cardiac arrest, myocardial infarction, or progressive heart failure.

Results During follow-up, 64 patients (23 percent) died, 47 (17 percent) of cardiac disease and 17 (6 percent) of other causes. The patients who died were older, weighed less, had poorer cardiac function, and had lower serum total and free T_3 concentrations, but similar serum total T_4, free T_4, and TSH concentrations, as compared with the patients who survived (Table).

Table. Clinical and Biochemical Findings in Patients with Heart Failure.

	Survived (n=217)	Died (n=64)
Women/men (n)	63/154	11/53
Age (mean yrs)	66	70*
Body mass index >30 kg/m^2	22 (10%)	10 (16%)
Amiodarone therapy	85 (39%)	20 (31%)
Ejection fraction	31%	26%*
End-diastolic diameter (mm)	61	64*
Serum TSH (mU/L)	1.9	2.3
Serum total T_3 (ng/dl)	84	65*
Serum free T_3 (ng/dl)	0.24	0.21*
Serum total T_4 (µg/dl)	9.8	8.1
Serum free T_4 (ng/dl)	1.4	1.4
Duration of follow-up (months)	14	8*

*P≤0.02.
Conversion factors: serum total T_3 × 0.0154 = nmol/L; free T_3 × 15.4 = pmol/L; total T_4 × 12.9 = nmol/L; and free T_4 × 12.9 = pmol/L.

Ejection fraction and serum total T_3 concentrations were not correlated with each other, but each was an independent predictor of all-cause and cardiac mortality. The survival rate among the 127 patients with an ejection fraction >20 percent and a serum total T_3 concentration >78 ng/dl (1.2 nmol/L) was 90 percent, and it was 61 percent in the 25 patients with an ejection fraction ≤20 percent and a serum total T_3 concentration ≤78 ng/dl (1.2 nmol/L). The rates were intermediate in the other 129 patients.

Conclusion A low serum total T_3 concentration independently predicts all-cause and cardiac mortality in patients with chronic heart failure.

COMMENTARY

Serum T_3 concentrations fall in everyone who is ill, or who is starved but otherwise well, caused by a decrease in extrathyroidal deiodinase activity, mostly type 1 deiodinase, that catalyzes conversion of T_4 to T_3. The magnitude of the fall varies considerably, but it roughly correlates with the severity of illness at that time. In this study, serum total T_3 concentrations were not correlated with ejection fraction when the patients were studied, and nothing is said about possible correlations with end-diastolic volume, New York Heart Association status (lower in the nonsurvivors), or amiodarone therapy, which lowers serum T_3 concentrations even in healthy people.

What is the meaning of studies like this, in which low serum T_3 concentrations are associated with mortality? If low serum T_3 concentrations are a beneficial adaptation to illness, then mortality should be lower in patients with low values, opposite to the results in this study. T_3 has inotropic and chronotropic effects, and therefore restoring normal serum T_3 concentrations acutely might have beneficial effects. If that were so, then at least early survival might be improved (and based on a Kaplan-Meier plot in the paper, most of the deaths in the low-ejection-fraction and low-serum-T_3 group were in the first three months). It is time to consider a low serum T_3 concentration, at least in patients with heart failure, as something more than a nonspecific indicator of illness.

Robert D. Utiger, M.D.

Tamoxifen decreased thyroid size in a patient with Riedel's thyroiditis

Jung YJ, Schaub CR, Rhodes R, Rich FA, Muehlenbein SJ. A case of Riedel's thyroiditis treated with tamoxifen: another successful outcome. Endocr Pract 2004;10:483-6.

SUMMARY

Background Riedel's thyroiditis (also known as invasive fibrous thyroiditis) is characterized by progressive fibrosis of the thyroid gland and surrounding tissues, which may lead to hypothyroidism, hypoparathyroidism, and compression or invasion of the trachea, recurrent laryngeal nerves, and other neck structures. Some patients have been treated by surgery, and some have improved when treated with a glucocorticoid or tamoxifen. This article describes a patient with Riedel's thyroiditis in whom administration of tamoxifen resulted in marked improvement.

Case Report The patient was a 40-year-old woman who was found to have a goiter (estimated to be 30 ml in volume) that was hard in consistency and overt hypothyroidism (serum thyrotropin [TSH], 203 mU/L; thyroxine [T_4], 0.3 μg/dl [3.9 nmol/L]) in May 2000. She was treated with T_4, in doses up to 175 μg daily, but the goiter increased. One year later, ultrasonography and magnetic resonance imaging revealed an enlarged heterogeneous thyroid gland. Her serum antithyroid peroxidase and antithyroglobulin antibody concentrations and the erythrocyte sedimentation rate were high.

The patient had increasing discomfort in her neck, and intermittent choking sensations, and further thyroid enlargement. Surgical exploration revealed very hard, whitish, immobile thyroid lobes. Anaplastic carcinoma was suspected, but frozen-section biopsy of the thyroid revealed only fibrous tissue. Permanent sections of the thyroid biopsy and a biopsy of a strap muscle revealed dense fibrous tissue and chronic inflammation, and no thyroid tissue, consistent with Riedel's thyroiditis. The fibrous tissue contained no estrogen receptors and only a few progesterone receptors, as determined by immunohistochemistry.

The patient was treated with tamoxifen, 20 mg twice daily, in addition to T_4. During a 19-month follow-up period, her thyroid gland progressively decreased in size, as determined by both physical examination and imaging.

Literature Review This article includes a table that summarizes the results of tamoxifen therapy in eight previously reported patients (six women, two men) with Riedel's thyroiditis (three patients received a glucocorticoid as well). All improved, in terms of both amelioration of symptoms such as stridor, sometimes in a few weeks, and a decrease in thyroid size, sometimes within a few months.

Conclusion Tamoxifen may be effective therapy in patients with Riedel's thyroiditis.

COMMENTARY

The cause of the fibrous-tissue proliferation, which often destroys and almost by definition extends beyond the thyroid and which defines Riedel's thyroiditis, is not known. In addition to the fibrosis, there is infiltration of mononuclear cells and neutrophils, including eosinophils (1), but not plasma cells. Some patients also have fibrous-tissue proliferation in the mediastinum and retroperitoneal space, sclerosing cholangitis, or pseudotumor of the orbits. The disorder may be distantly related to desmoid tumors (it was the efficacy of tamoxifen in patients with these tumors that led to its use in patients with Riedel's thyroiditis [2]). In addition to hypothyroidism, many of the patients have high serum antithyroid antibody concentrations, probably as a result of autoimmunization after thyroid injury rather than true autoimmune thyroiditis. The differential diagnosis includes the fibrous variant of Hashimoto's thyroiditis; subacute granulomatous thyroiditis; perhaps also amyloid goiter, scleroderma and histiocytosis X of the thyroid; and anaplastic thyroid carcinoma. These disorders are confined to the thyroid, excepting anaplastic carcinoma, and its growth rate is more rapid than that of Riedel's thyroiditis.

The diagnosis of Riedel's thyroiditis can sometimes be made on the basis of clinical and imaging findings, but fine-needle aspiration biopsy (3) or even open biopsy may be needed. The disorder tends to be slowly progressive, but may stabilize or even regress spontaneously. Many patients are treated with T_4, but it rarely decreases thyroid size or relieves the symptoms that result from compression of structures in the neck. Some patients need surgical decompression of their airway or other structures, but resection is at best palliative and is hazardous. Glucocorticoids may decrease thyroid size or relieve symptoms, but sometimes have no or only a transient effect. Tamoxifen seems to be effective, sometimes resulting in a marked decrease in thyroid size (2), and no patients who did not respond to tamoxifen have been described, but that may be negative publication bias. How it alters the underlying process is not known; one hypothesis is that it stimulates cellular production of transforming growth factor-β, which inhibits the growth of fibroblasts (1).

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A high dose of methimazole has little antithyroid effect in patients with psoriasis

Hasegawa M, Abe M, Ohnishi K, Shoji C, Ishikawa O. Clinical usefulness of a long-term treatment with an antithyroid drug for psoriasis vulgaris. J Dermatol 2004;31:794-7.

SUMMARY

Background Short-term studies have suggested that antithyroid drugs may be effective therapy in patients with psoriasis. This benefit has been thought to be due to an immunomodulatory action of the drug, rather than to its antithyroid action. This study was done to determine the long-term efficacy and effects of a high dose of methimazole in patients with psoriasis.

Methods The study subjects were eight patients (one woman, seven men; mean age, 36 years [range, 22 to 62]) with long-standing psoriasis (mean duration, 15 years). They were treated with 30 mg of methimazole daily for 12 weeks (the dose was reduced to 20 mg daily in 3 patients after 8 to 10 weeks because they had a >85 percent decrease in the Psoriasis Area and Severity Index). The patients were evaluated and serum thyrotropin (TSH), free thyroxine (T_4), and free triiodothyronine (T_3) were measured at base line, during treatment, and at the end of treatment.

Results During the 12-week treatment period, five of the eight patients had a complete remission or moderate to marked improvement in psoriasis, one slight improvement, and two no improvement. Two patients had pruritus and one had high serum aminotransfersase concentrations during treatment.

At base line, all the patients had normal serum TSH, free T_4, and free T_3 concentrations. During treatment, no patient had any clinical manifestations of hypothyroidism. Serum free T_4 and free T_3 concentrations remained within the normal range in all patients. Serum TSH decreased in one patient, did not change in four patients, and increased in three patients, two of whom were treated with T_4 (values not given).

Conclusion In patients with psoriasis, methimazole, in a dose of 30 mg daily for 12 weeks, was effective and had little antithyroid activity.

COMMENTARY

Psoriasis is thought to have an autoimmune component, and methimazole and propylthiouracil are thought to have immunomodulatory activity. These thoughts underlie the administration of these drugs to patients with psoriasis. The two drugs have also been thought to have immunomodulatory activity in patients with hyperthyroidism caused by Graves' disease, but that is controversial, and will not be discussed further here.

There have been scattered reports of treatment of psoriasis with these drugs in the dermatology literature for over a decade. The doses have been as high as 40 mg of methimazole daily for 8 weeks and 300 mg of propylthiouracil daily for 12 weeks (1). As in this study, few patients have had any changes in thyroid function. There are no hormonal results in this paper, but nonetheless the patients received a lot of methimazole for a lengthy period, with little antithyroid effect.

Consider the following: in a study of 420 patients with overt hyperthyroidism caused by Graves' disease, 204 were treated with 10 mg of methimazole daily; among them 86 (42 percent) were euthyroid in 3 weeks, 158 (77 percent) were euthyroid in 6 weeks, and 189 (93 percent) were euthyroid in 12 weeks. (The other 216 patients were treated with 40 mg of methimazole daily; among them 140 [65] percent) were euthyroid in 3 weeks, 200 [92 percent] were euthyroid in 6 weeks, and 212 [98 percent] were euthyroid in 12 weeks [2]). The rapid and substantial effect of a low dose of methimazole in this study of patients with hyperthyroidism is not an isolated result; in several other studies many patients treated with 15 mg of methimazole daily were euthyroid in 8 weeks. Finally, in some patients with Graves' hyperthyroidism doses as low as 5 mg of methimazole daily caused hypothyroidism, and doses of 2.5 mg daily were sufficient to prevent hyperthyroidism (3).

Factors that could alter the efficacy of methimazole in patients with hyperthyroidism include iodide intake (the drug is more effective when iodide intake is low [4]), the severity of hyperthyroidism (plasma drug clearance is not altered by hyperthyroidism, but intrathyroidal clearance could be faster), thyroid size (more drug needed to maintain a high intrathyroidal drug concentration), and, in those with Graves' disease, immunomodulatory activity, if indeed the drug has this activity.

None of these factors seems to explain why 30 mg of methimazole daily did so little in these patients with psoriasis. Is it possible that the stimulated thyroid takes up more methimazole or is somehow more sensitive to it that the normal thyroid? That seems unlikely, but….

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The antituberculosis drug rifampin can cause hypothyroidism in patients with Hashimoto's thyroiditis

Takasu N, Takara M, Komiya I. Rifampin-induced hypothyroidism in patients with Hashimoto's thyroiditis. N Engl J Med 2005;352:518-9.

SUMMARY

Background Some drugs accelerate the clearance of thyroxine (T_4). In normal subjects, T_4 production increases sufficiently to maintain normal serum T_4 concentrations, but it may not in patients with thyroid disease, as reported in three patients treated with rifampin.

Case Reports Three euthyroid patients with Hashimoto's thyroiditis developed hypothyroidism when treated with rifampin for tuberculosis. They were treated with T_4, and later remained euthyroid for varying intervals after both rifampin and T_4 were stopped.

Case 1 A 62-year-old man with non-Hodgkin's lymphoma in remission was hospitalized because he had a productive cough. His serum thyrotropin (TSH) concentration was normal (2.0 and 2.4 mU/L), but he had a high serum antithyroid peroxidase (TPO) antibody concentration (28 U/ml [normal, <6.7]) and a high antithyroglobulin (Tg) antibody concentration (42 U/ml [normal, <2.6]). He was found to have pulmonary tuberculosis, and was treated with rifampin. Two weeks later, he had a high serum TSH concentration (170 mU/L) and a low serum T_4 concentration (2.4 μg/dl [31 nmol/L]). He was treated with T_4. Later, after rifampin was stopped, T_4 was stopped, and he remained euthyroid during a 4-month follow-up period.

Case 2 A 66-year-old woman with ascites was found to have tuberculous peritonitis. She was euthyroid, but had a goiter and high serum anti-TPO and anti-Tg antibody concentrations (10 U/ml and 54 U/ml, respectively). She was treated with rifampin, and developed hypothyroidism (serum TSH, 12.5 mU/L; serum T_4, 4.8 μg/dl [62 nmol/L]). She was treated with T_4 for three months. Hypothyroidism recurred, and she was treated with T_4 until the rifampin was stopped. Thereafter, she remained euthyroid for 42 months.

Case 3 A 56-year-old woman with a hepatic abscess and lymphadenopathy had a lymph-node biopsy that revealed tuberculous granulomas. She was euthyroid (serum TSH concentrations, 3.2 and 3.9 mU/L), but had a goiter. Her serum anti-TPO and anti-Tg antibody concentrations were 5.6 U/ml and 19 U/ml, respectively. She was treated with rifampin; two weeks later her serum TSH concentration was 21.3 mU/L, and she was treated with T_4. Rifampin and then T_4 were stopped, and she remained euthyroid. Three weeks later, rifampin was resumed, and four weeks after that she again had hypothyroidism and was treated with T_4. The rifampin and T_4 were stopped 7 months later, and she remained euthyroid for 12 months.

Conclusion In patients with Hashimoto's thyroiditis, the antituberculosis drug rifampin can cause hypothyroidism, which subsides when the rifampin is stopped.

COMMENTARY

Rifampin is a potent inducer of mixed-function oxygenases and other hepatic enzymes. As such, it increases the rate of clearance of T_4, at least in part because it increases the rate of glucuronidation of T_4 (1,2). The resulting fall in serum T_4 concentrations is counterbalanced by an increase in T_4 production, which can be estimated to be from 20 to 40 μg daily. This increase must be mediated by an increase in TSH secretion; alternatively, some intrathyroidal autoregulation increases thyroid sensitivity to TSH. Serum T_3 concentrations do not change; T_4 glucuronide cannot be converted to T_3, and T_3 itself is a poor substrate for glucuronidation.

Serum TSH concentrations rise in T_4-treated patients with hypothyroidism when they are given rifampin, because they have no functional thyroid reserve (3). The induction of hypothyroidism by rifampin in the three patients with Hashimoto's thyroiditis described by Takasu et al. indicates that they had little functional thyroid reserve. Given that all the patients were euthyroid initially, the striking differences in their serum TSH concentrations during rifampin therapy suggests that there were variations in the acceleration of T_4 clearance induced by the drug and perhaps also variations in thyroid reserve. Presumably, the man whose serum TSH concentration increased to 170 mU/L had a greater fall in serum T_4 concentration, as a result of a greater effect of rifampin on T_4 clearance, than did the other patients. Whether other anti-tuberculous drugs were given is not mentioned, and therefore the possibility of their contributing to the changes cannot be excluded.

Rifampin is likely to have the same effect in any euthyroid patient with limited thyroid reserve, for example, patients who have had a subtotal thyroidectomy or been treated with radioiodine, or indeed patients with any thyroid injury. The effect is not limited to rifampin. Phenytoin and carbamazepine also increase T_4 clearance, and therefore could induce hypothyroidism in similar patients.

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Children with vitamin A and iodine deficiency have higher serum thyrotropin and thyroxine concentrations than children with iodine deficiency

Zimmermann MB, Wegmuller R, Zeder C, Chaouki N, Torresani T. The effects of vitamin A deficiency and vitamin A supplementation on thyroid function in goitrous children. J Clin Endocrinol Metab 2004;89:5441-7.

SUMMARY

Background Worldwide, both iodine deficiency and vitamin A deficiency are common. When they coexist, the risk of thyroid dysfunction and goiter may be increased, as compared with iodine deficiency alone. In this study the effects of iodine and vitamin A deficiency on thyroid function were determined in a group of Moroccan children. The children were then studied after iodine supplementation with and without vitamin A supplementation.

Methods The initial study subjects were 298 children 6 to 14 years old (136 girls, 162 boys; mean age, 10 years) attending three schools in rural northern Morocco. Their overall nutrition was considered adequate (mean weight, 29.7 kg; mean height, 1.34 m), and none had ophthalmic signs of vitamin A deficiency (xerophthalmia). Thyroid volume was measured by ultrasonography. Iodine was measured in spot urine samples, thyrotropin (TSH) in blood spots, and retinol, thyroxine (T_4), and thyroglobulin in serum. Vitamin A deficiency was defined as a serum retinol value <20 μg/dl (0.70 μmol/L), and low vitamin A status as a serum retinol value of 20 to <30 μg/dl (1.05 μmol/L).

The supplementation study was done in all 138 children (72 girls, 66 boys; mean age, 10 years) with vitamin A deficiency or low vitamin A status attending two of the schools. They were randomly divided by household into two groups. One was given 200,000 IU of vitamin A, as retinyl palmitate, and the other a placebo at base line and 5 months; the households of both groups were provided with salt fortified with iodine (25 μg/g). The tests described above were repeated at 10 months.

Results Among the 298 children in the cross-sectional study, 265 (89 percent) had a goiter and their mean urinary iodine excretion was 10 μg/L (0.08 μmol/L). Their median blood-spot TSH concentration was 1.5 mU/L (range, 0.3 to 120), mean serum T_4 concentration was 7.4 μg/dl (96 nmol/L), and median serum thyroglobulin concentration was 56 ng/ml (range, 1 to 788). Their mean (±SD) retinol concentration was 27.2±0.7.2 μg/dl (0.95±0.25 μmol/L); 50 (17 percent) had vitamin A deficiency, and 149 (50 percent) had low vitamin A status. Log blood-spot TSH, log serum T_4 and thyroglobulin concentrations, and log thyroid volume were negatively correlated with serum retinol concentrations ($P<0.01$). Thus, vitamin A deficiency was associated with higher blood-spot TSH concentrations, higher serum T_4 and thyroglobulin concentrations, and more thyroid enlargement (Table).

Table. Thyroid Function and Goiter in 298 Children According to Vitamin A Status.

	Vitamin A Deficiency	Low Vitamin A Status	Adequate Vitamin A
Serum T4			
<5.0 μg/dl*	0 (0%)	7 (2%)	38 (13%)
≥5.0 μg/dl	50 (17%)	142 (48%)	61 (20%)
Serum TSH			
>3.7 mU/L	40 (13%)	1 (0.3%)	0 (0%)
≤3.7 mU/L	10 (3%)	148 (50%)	99 (33%)
Goiter			
Present	9 (16%)	141 (47%)	75 (25%)
Absent	1 (0.3%)	8 (3%)	24 (8%)

*To convert to nmol/L, multiply by 12.9.

The base-line characteristics of the children in the two treatment groups were similar. At 10 months, urinary iodine excretion increased approximately 10-fold in both groups, and vitamin A status markedly improved in the vitamin A group. The median blood-spot TSH value decreased more in the iodine-vitamin A group (2.3 to 0.9 mU/L) than in the iodine-placebo group (2.1 to 1.6 mU/L), as did thyroid volume (7.2 to 5.3 ml vs. 7.4 to 6.2 ml), frequency of goiter, and serum thyroglobulin concentrations. Serum T_4 concentrations increased slightly in both groups (by 7 and 6 percent).

Conclusion Children with iodine deficiency and vitamin A deficiency have higher TSH and T_4 concentrations and more thyroid enlargement, as compared with children with iodine deficiency alone. Supplementation with both is more effective in reversing the changes of iodine deficiency than is supplementation with iodine alone.

COMMENTARY

Vitamin A metabolism and transport are intermingled with those of T_4 in several ways. In serum, some T_4 is bound to transthyretin, and it also binds retinol-binding protein. Serum retinol-binding protein, as well as retinol, concentrations were low in these children with vitamin A deficiency, but their serum transthyretin (and thyroxine-binding globulin) concentrations were normal, and did not change during vitamin A supplementation. Therefore, vitamin A deficiency does not alter T_4 transport.

It does, however, alter the pituitary response to iodine deficiency, resulting in greater TSH secretion, and therefore greater T_4 and thyroglobulin secretion and more thyroid enlargement, as compared with iodine deficiency alone. The explanation lies in the fact that complexes of retinoic acid (retinol) and retinoid X receptors inhibit TSH secretion (via inhibition of the gene for the β-subunit of TSH); thus, in the absence of retinoic acid, more TSH is produced at any given level of T_4 production. And so thyroid secretion is better maintained, albeit with more thyroid enlargement. Given these effects, iodine intake—if at all inadequate—should be supplemented whenever vitamin A is supplemented.

Robert D. Utiger, M.D.

Review Articles

Bojunga J, Zeuzem S. Molecular detection of thyroid cancer: an update. Clin Endocrinol (Oxf) 2004;61:523-30.

Leboulleux S, Baudin E, Travagli JP, Schlumberger M. Medullary thyroid carcinoma. Clin Endocrinol (Oxf) 2004;61:299-310.

Lin SH. Thyrotoxic periodic paralysis. Mayo Clin Proc 2005;80:99-105.

Mandel SJ. A 64-year-old woman with a thyroid nodule. JAMA 2004;292:2632-42.

Robbins RJ, Schlumberger MJ. The evolving role of ^{131}I for the treatment of differentiated thyroid carcinoma. J Nucl Med 2005;45:28S-37S.

Corrections

Male sex and increasing age are the major risk factors for atrial fibrillation in patients with hyperthyroidism (November 2004:42). The sentence describing the frequency of other disorders (left column, Results section), should read: "Eight percent had hypertension, 11 percent had ischemic heart disease, 1 percent had valvular heart disease, 6 percent had heart failure, and 5 percent had diabetes."

The Table also contains errors. The correct values are:

Table. Risk Factors for Atrial Fibrillation among Patients with Hyperthyroidism.

	Adjusted Odds Ratio*
Men—women as reference group	1.7 (1.6-1.9)
Age at diagnosis of hyperthyroidism—per 10-year increment	1.7 (1.7-1.8)
Comorbidity—no comorbidity as reference group	
Hypertension	0.9 (0.8-1.0)
Ischemic heart disease	1.3 (1.2-1.4)
Valvular heart disease	1.9 (1.5-2.4)
Heart failure	2.8 (2.6-3.1)
Diabetes mellitus	0.9 (0.8-1.1)

*Adjusted for the other characteristics listed, with 95 percent confidence interval.

These errors do not alter the conclusions of the study. (Erratum published in Arch Intern Med 2005;165:307.)

Subclinical hypothyroidism may progress to overt hypothyroidism or disappear (November 2004:47). There is an error—duplication of the number 37—in line 2 of the table.

CLINICAL THYROIDOLOGY

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