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ATA News

Future Meetings

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September 16 to 21, 2003
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Palm Beach, FL

76th Annual Meeting
September 29 to October 3, 2004
Westin Bayshore Resort and Marina
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The dietary supplement tiratricol (3,5,3′-triiodothyroacetic acid) can cause symptoms of hyperthyroidism

Bauer BA, Elkin PL, Erickson D, Klee GG, Brennan MD. Symptomatic hyperthyroidism in a patient taking the dietary supplement tiratricol. Mayo Clin Proc 2002;77:587-90.

SUMMARY

Background Tiratricol (3,5,3′-triiodothyroacetic acid, or triac) is a metabolite of thyroxine (T_4) that has some intrinsic thyromimetic activity. It is marketed in health food stores and on the Internet as a substance that accelerates metabolism and burns fat. This paper describes a patient in whom tiratricol caused symptoms of hyperthyroidism.

Case Report The patient was an 87-year-old woman who was referred to the Mayo Clinic in May 2001. Four months earlier she was told by a chiropractor that she had a mild anemia, and she had been advised to take multiple dietary supplements (Osteo-Genics, Hemagenics, Serenagen, Bio Pure Protein, Acida-Zyme, Therazyme, *Ginkgo biloba*, multivitamins, and tiratricol). The dose of tiratricol was three 1000-μg tablets daily. Two months later, she noted the onset of persistent nervousness, insomnia, tremor, fatigue, and weight loss. Physical examination, including examination of the thyroid, was normal. Her serum thyrotropin (TSH) concentration was 0.015 mU/L (normal, 0.3 to 5.0), her serum free T_4 concentration was low (0.6 ng/dL [7.7 pmol/L]), and her serum triiodothyronine (T_3) concentration was high (293 ng/dL [4.5 nmol/L]). Tiratricol was not tested, but 3,5,3′-triiodothyropropionic acid had 33 percent cross-reactivity in the serum T_3 assay. (Six months earlier her serum TSH concentration had been 2.9 mU/L and her serum total T_4 concentration 6.2 μg/dL ([80 nmol/L]).

The patient was advised to stop taking all the dietary supplements. Her symptoms disappeared, and four weeks later her serum TSH concentration was 5.9 mU/L and her serum free T_4 and T_3 concentrations were normal. She then resumed taking all the supplements except tiratricol. Her symptoms did not recur, and six weeks later the tests of thyroid function were normal.

Conclusion Tiratricol is a thyroid hormone analogue that can be purchased as a dietary supplement and can cause symptoms of hyperthyroidism.

COMMENTARY

There is a long list of natural products euphemistically called dietary or nutritional supplements that affect thyroid hormone production or action, and that therefore can cause hypothyroidism or hyperthyroidism. One group of products are those that contain large amounts of iodine, such as kelp, that can increase or decrease thyroid hormone production in patients with different thyroid disorders. A second consists of products rich in tyrosine. These are marketed on the grounds that tyrosine is an essential substrate for thyroid hormone production, and therefore an increase in tyrosine intake will increase thyroid hormone production. This is a classic half-truth; tyrosine is of course needed for thyroid hormone production, but there is no evidence that feeding tyrosine increases thyroid hormone production in anybody. A third consists of crude thyroid extracts and purified T_4 analogs such as tiratricol. These substances are marketed not only as dietary or nutritional supplements, but also as fat burners. They have thyromimetic actions, and therefore can cause hyperthyroidism, if taken in sufficient quantities (1), but they can hardly be called dietary or nutritional supplements, and there is no evidence that they stimulate fat catabolism, as they are advertised to do.

Tiratricol binds well to thyroid hormone receptors in vitro, but has about 5 to 10 percent of the calorigenic activity of T_3 in vivo. In studies in patients with thyroid carcinoma and severe hypothyroidism, the mean doses of T_4 and tiratricol needed to reduce serum TSH concentrations to just below 0.1 mU/L were 2.2 μg/kg/day and 48 μg/kg/day (ratio, 1:22), respectively (2). As compared with T_4, tiratricol had similar effects on a thyrotoxicosis symptom score, body weight, resting metabolic rate, fat oxidation, and urinary nitrogen excretion, but it had relatively greater effects on the liver and skeleton (2). The patients given tiratricol had undetectable serum free T_4 concentrations.

Tiratricol is undeniably a natural product, but to call it a dietary or nutritional supplement is surely a misnomer. The FDA has banned several tiratricol products, but as of November 4, 2002, it remains available at at least one Web site (www.muscleshop.net/TriCuts.htm). There, ninety 1000-μg tablets of tiratricol can be purchased for $79.99. The suggested dose is 3000 μg daily. This is enough to provide a 62.5-kg person with the 48 μg/kg/day needed to cause at least mild hyperthyroidism. There is no reason to think that tiratricol has unique properties as a "fat burner"; it is just another way of selling thyroid hormone and at the same time evading regulation by the Food and Drug Administration.

Robert D. Utiger, M.D.

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1. Eliason BC, Doenier JA, Nuhlicek DN. Desiccated thyroid in a nutritional supplement. J Fam Pract 1994;38:287-8.

2. Sherman SI, Ringel MD, Smith MJ, et al. Augmented hepatic and skeletal thyromimetic effects of tiratricol in comparison with levothyroxine. J Clin Endocrinol Metab 1997;82:2153-8.

The serum free triiodothyronine to free thyroxine ratio and the peripheral blood eosinophil to monocyte ratio help to distinguish between Graves' disease and thyroiditis as a cause of thyrotoxicosis

Izumi Y, Hidaka Y, Tada H, Takano T, Kashiwai T, Tatsumi K, Ichihara K, Amino N. Simple and practical parameters for differentiation between destruction-induced thyrotoxicosis and Graves' thyrotoxicosis. Clin Endocrinol 2002;57:51-8.

SUMMARY

Background Differentiating between thyrotoxicosis caused by silent (painless) thyroiditis and Graves' disease is important, because the natural history and treatment of the two disorders differ. They can be differentiated on the basis of measurements of thyroid radioiodine uptake and thyrotropin (TSH)-receptor antibodies in serum, but simpler tests are needed. This study evaluated the efficacy of measurements of the molar ratio of free triiodothyronine (T_3) to free thyroxine (T_4) in serum and the ratio of peripheral blood eosinophils to monocytes to differentiate between silent thyroiditis and also subacute thyroiditis and Graves' disease as causes of thyrotoxicosis.

Methods The study subjects were 111 patients with thyrotoxicosis. They included 69 patients (52 women, 17 men; mean [±SD] age, 37±13 years) with Graves' disease, 21 patients (17 women, 4 men; mean age, 41±14 years) with painless thyroiditis, and 21 patients (17 women, 4 men; mean age, 48±7 years) with subacute (painful) thyroiditis. All the patients had high serum free T_3 and free T_4 concentrations. The diagnosis of Graves' disease was based on a positive test for TSH receptor antibodies or a high thyroid radioiodine uptake. Painless thyroiditis was diagnosed on the basis of high serum free T_3 and free T_4 concentrations for less than three months, and a low thyroid radioiodine uptake or later development of transient hypothyroidism. Subacute thyroiditis was diagnosed on the basis of neck pain and tenderness, fever, neck swelling, a high serum C-reactive protein or low thyroid radioiodine uptake value, and spontaneous remission of thyroid dysfunction. Serum free T_3 and free T_4 were measured by radioimmunoassay and blood eosinophils and monocytes by an automated method before any treatment was given.

Results The mean serum free T_3 and free T_4 concentrations in the patients with Graves' disease were 1.3±0.6 ng/dL (20±10 pmol/L) and 4.0±1.9 ng/dL (51±25 pmol/L), respectively, as compared with 0.8±0.5 ng/dL (12±8 pmol/L) and 3.0±2.4 ng/dL (39±31 pmol/L, respectively, in the patients with painless thyroiditis. The values in the patients with subacute thyroiditis were similar to those in the patients with painless thyroiditis. The serum free T_3:free T_4 molar ratio was higher in the patients with Graves' disease (0.40±0.09) than in the patients with either painless thyroiditis (0.30±0.07, P<0.01) or subacute thyroiditis (0.34±0.06, P<0.01). Among the 28 patients with thyrotoxicosis who had a serum free T_3:free T_4 molar ratio <0.3, 22 (79 percent) had silent or subacute thyroiditis (Table).

Table. Test Results Distinguishing Thyrotoxicosis Caused by Graves' Disease and Thyrotoxicosis Caused by Painless or Subacute Thyroiditis.

	Cutoff Value	Graves' Disease (n=69)	Thyroiditis (n=42)	Proportion with Graves' Disease	Proportion with Thyroiditis
Serum free T_3: free T_4 ratio	<0.3	6	22	21%	79%
Eosinophil: monocyte ratio	>1.0	15	0	100%	0%
	<0.2	2	22	8%	92%

The mean percentage of eosinophils was 3.5 in the patients with Graves' disease, as compared with approximately 1.4 in the patients with silent thyroiditis (P<0.01) and 1.1 in the patients with subacute thyroiditis (P<0.01). The mean eosinophil:monocyte ratios were 0.8±0.8 in the patients with Graves' disease, 0.3±0.2 in the patients with silent thyroiditis (P<0.01), and 0.2±0.2 in the patients with subacute thyroiditis (P<0.01). Among the 24 patients with thyrotoxicosis who had an eosinophil:monocyte ratio <0.2, 22 (92 percent) had silent or subacute thyroiditis (Table).

Conclusion Measurements of the serum free T_3:free T_4 molar ratio and the peripheral blood eosinophil:monocyte ratio distinguish between Graves' disease and silent thyroiditis or subacute thyroiditis as causes of thyrotoxicosis.

COMMENTARY

Distinguishing between Graves' disease and silent thyroiditis, whether it occurs postpartum or unrelated to pregnancy, as a cause of thyrotoxicosis may be difficult, and simple blood tests that distinguished between the two disorders would be useful.

The evaluation of eosinophil and monocyte counts as indicators of the cause of thyrotoxicosis was based on the association between Graves' disease and humoral immunity (Th2-cell predominance), which is associated with eosinophilia, and the association between silent thyroiditis and subacute thyroiditis with cellular immunity (Th1-cell predominance), which is associated with mononuclear cells. It is easy to count these cells, but the differences in cell counts and the eosinophil:monocyte ratio were small, and no information about the day-to-day reproducibility of the counts was provided. Also, thyroid radioiodine uptake was not measured routinely, so that the hormone and cell count ratios cannot be compared with the test used most widely to distinguish between these disorders.

Robert D. Utiger, M.D.

Concordance of Graves' disease is greater in monozygotic than dizygotic twins

Ringold DA, Nicoloff JT, Kesler M, Davis H, Hamilton A, Mack T. Further evidence for a strong genetic influence on the development of autoimmune thyroid disease: the California Twin Study. Thyroid 2002;12:647-53.

SUMMARY

Background There is strong evidence for genetic susceptibility to Graves' disease, based on studies of twins, family clustering, and gene linkage, but the extent of heritability has varied in different studies. In this study the heritability of Graves' disease was determined in a large cohort of monozygotic and dizygotic twins.

Methods The California Twin Program was created as a file of all twins born in the state from 1908 to 1982. This file was linked to the state's file of people who had active driver's licenses in 1991, which yielded 102,000 twins. A questionnaire was sent to the 36,244 twins aged 40 years or older. The twins were asked about their personal characteristics and medical history, including questions about Graves' disease and other thyroid disorders in themselves, their cotwins, and other family members, including spouses. Usable questionnaires were returned by 19,378 subjects (53 percent), representing 13,708 twin pairs. Based on the self-reports of these respondents, 32 percent were monozygotic twins (50 percent women, 50 percent men), 37 percent were like-sex dizygotic twins (17 percent women, 20 percent men), and 31 percent were unlike-sex dizygotic twin pairs. The mean ages of these five groups ranged from 44 to 50 years.

The subjects reporting a diagnosis of Graves' disease or other thyroid disorder were interviewed by telephone, at which time they were asked detailed questions about symptoms and signs of hyperthyroidism, the basis for diagnosis, treatment, and course, and also the presence of Graves' ophthalmopathy in themselves, their twins, and other family members. An investigator who was unaware of individual identity and twin status reviewed each questionnaire and confirmed the diagnosis of Graves' disease.

Results On the basis of the initial questionnaire, a diagnosis of Graves' disease was suggested in 118 members of 110 twin pairs. Information was available from both twins of 62 twin pairs, of whom 70 reported Graves' disease, and one twin of 48 twin pairs, of whom 35 reported Graves' disease in themselves and 13 in their twin.

Among these 118 subjects, 106 (77 women, 29 men) were confirmed to have Graves' disease after the telephone interview. Ten of these subjects had no twin at risk, because of death or thyroidectomy. There were 89 twin pairs in which one or both twins were confirmed to have Graves' disease. They included 35 pairs of monozygotic twins, among which 6 pairs (17 percent) were concordant for Graves' disease (5 female pairs, 1 male pair), and 54 pairs of dizygotic twins, among which 1 twin pair (2 percent) was concordant for Graves' disease (1 female, 1 male). The mean age at diagnosis in the concordant pairs was 33 years (range, 12 to 46), and the mean interval between diagnosis in each member of a pair was 12 years. In 5 of the 35 monozygotic twin pairs (14 percent) and 1 of the 54 dizygotic twin pairs (2 percent), one twin had Graves' disease and the other twin had chronic autoimmune thyroiditis.

Among the twins with Graves' disease, none had a spouse reported to have Graves' disease, but 19 of 488 first-degree relatives (4 percent) did have the disease.

Conclusion Among twins in California, Graves' disease was more common in monozygotic than dizygotic twins, confirming that the disease has a heritable component.

COMMENTARY

The results of this study mirror those of a 1998 study of twins in Denmark (pairwise concordance rate, 22 percent for monozygotic twins, 0 percent for dizygotic twins) (1); in earlier studies the rates in both types of twins were higher (reviewed in 1). Some of the variations can be explained by variations in the ages of the twins when surveyed; accuracy of recall; variations in questionnaires; criteria for diagnosis; and extent of documentation of diagnosis. Of course, Graves' disease is not synonymous with hyperthyroidism, but it is nearly enough so in common parlance that asking about Graves' disease can be considered asking about hyperthyroidism, and vice-versa, at least in the United States.

The nature of the genetic susceptibility to Graves' disease revealed by twin and other studies is not known. The disease has been linked to genes that affect the thyroid and genes that affect immune regulation. Therefore, the heritable components of the disease are almost certainly polygenic. The nature of the non-heritable contributions to the disease, whether as risk factors or actual precipitating factors, is equally if not more uncertain, and they too are surely multiple.

Robert D. Utiger, M.D.

Reference

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Shedding of part of the thyrotropin receptor may be important in the pathogenesis of hyperthyroidism in Graves' disease

Chazenbalk GD, Pichurin P, Chen CR, Latrofa F, Johnstone AP, McLachlan SM, Rapoport B. Thyroid-stimulating autoantibodies in Graves' disease preferentially recognize the free A subunit, not the thyrotropin holoreceptor. J Clin Invest 2002;110:209-17.

SUMMARY

Background The proximate cause of hyperthyroidism in patients with Graves' disease is activation of thyrotropin (TSH) receptors on thyroid follicular cells by TSH receptor-stimulating antibodies (TSHR-SAb). These receptors are composed of an extracellular amino-terminal domain and a transmembrane and intracellular domain. After insertion into the cell membrane the extracellular domain can be cleaved in two places, forming an A subunit (Figure) and a B subunit, which are joined by disulfide bonds, and the intervening C peptide region is deleted. The binding site (and epitope) for TSHR-SAb and the binding site for TSH overlap each other at the amino-terminal end of the A subunit. The A subunit is shed from the receptor into the extracellular fluid. This study was done to determine the reactivity of different forms of the receptor with TSH, TSHR-SAb, and TSH receptor-blocking antibodies (TSHR-BAb).

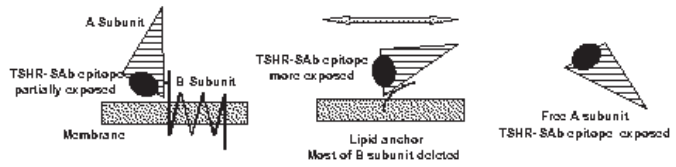

Figure. Schematic Diagram of TSH Receptors Showing the Intact Receptor (TSHR) (Left), the Extracellular Domain Anchored to Cells (ECD-TSHR) (Middle), and the Free A Subunit (Right). (Drawing kindly supplied by the authors.) Black ovals, TSHR-SAb epitope; horizontal lined triangles, A subunit.

Methods Intact uncleaved TSH receptors (TSHR cells) or the extracellular domain of the receptor anchored to the cell membrane with glycosylphosphatidylinositol (ECD-TSHR cells) were expressed in hamster ovary cells. The cells were incubated with a monoclonal antibody (3BD10) that reacts with the amino terminus of the A subunit (amino acid residues 25-51), a monoclonal antibody (2C11) that reacts with the C peptide region (amino acids 354-359), and serum samples from 20 patients with Graves' hyperthyroidism containing TSHR-SAb, 7 patients with hypothyroidism containing TSHR-BAb, and 9 normal subjects. The cells were then incubated with fluorescein-labeled antimouse or anti-human immunoglobulin and the extent of binding measured by flow cytometry. The ability of free A subunit to inhibit binding was also tested.

Results The ECD-TSHR cells bound more 3BD10 antibody than did the TSHR cells, suggesting that the epitope for the 3BD10 antibody was more exposed in the ECD-TSHR cells. In contrast, the TSHR cells bound more 2C11 antibody, because these cells contained more receptor than did the ECD-TSHR cells, as documented by binding of radiolabeled TSH. Serum from 17 of the 20 patients with Graves' hyperthyroidism bound to ECD-TSHR cells better than to TSHR cells, despite the greater number of receptors on the TSHR cells. In contrast, serum from patients with hypothyroidism bound equally well to both types of cells. Serum from normal subjects did not bind to either type of cell. Preincubation of A subunit with serum from patients with Graves' hyperthyroidism abolished serum binding to cells, whereas the effect of preincubation of A subunit with serum from patients with hypothyroidism was variable.

Conclusion TSHR-SAb in serum from patients with Graves' hyperthyroidism bind preferentially to exposed TSH receptors, as compared with intact receptors, and binding is readily inhibited by the A subunit. Exposure to A subunit as a result of its natural shedding into extracellular fluid may be important in the pathogenesis of the disease.

COMMENTARY

Previous studies of the reactivity of TSHR-SAb have suggested that the antibodies bind primarily to discontinuous segments of the amino-terminal domain of the TSH receptor (1), indicating that both conformation of the receptor and its amino-acid sequence are determinants of antibody reactivity; in other words the epitopes are conformational and structural. The present work extends this suggestion, by demonstrating differences in TSHR-SAb reactivity with cells in which the amino-terminal end of the receptor had a different conformation.

What is perhaps surprising was that cells with intact receptors bound TSHR-SAb less well than cells with incomplete but possibly more exposed receptors. These results, plus the neutralization studies, plus the fact that the A subunit is shed and therefore has easy access to antigen-processing cells, all support a very prominent role for the A subunit in the generation and continued production of TSHR-SAb. As the authors note, further support for a prominent role for the shed A subunit comes from the fact that among the receptors for glycoprotein hormones (TSH, luteinizing hormone, follicle-stimulating hormone, chorionic gonadotropin), only TSH receptor are cleaved and shed, and there are no disorders of the gonads or placenta characterized by production of antibodies that activate the receptors for the gonadotropins.

Robert D. Utiger, M.D.

Reference

1. Rapoport B, Chazenbalk GD, Jaume JC, et al. The thyrotropin (TSH) receptor: interaction with TSH and autoantibodies. Endocr Rev 1998;19:673-716.

Neonatal hyperthyroidism occurs only in infants whose mothers have very high serum thytropin receptor-stimulating antibody concentrations

Peleg D, Cada S, Peleg A, Ben-Ami M. The relationship between maternal serum thyroid-stimulating immunoglobulins and fetal and neonatal thyrotoxicosis. Obstet Gynecol 2002;99:1040-3.

SUMMARY

Background Fetuses and neonates of mothers who have hyperthyroidism caused by Graves' disease may have hyperthyroidism, caused by the transplacental passage of thyrotropin (TSH) receptor-stimulating antibodies. This study was done to determine the relationship between maternal serum concentrations of these antibodies and the likelihood of fetal or neonatal hyperthyroidism.

Methods From 1986 to 1995, serum TSH receptor-stimulating antibodies (in the form of thyroid-stimulating immunoglobulins) were measured in 61 pregnant women in a single laboratory. These measurements were done at the discretion of the patient's physician, using a bioassay in which immunoglobulins extracted from serum were incubated with cultured rat thyroid cells and the amount of cyclic AMP generated was determined. The results were expressed as index units; 1 index unit was defined as the amount of cyclic AMP generated in the presence of a pool of serum immunoglobulins from normal subjects, and an index value >1.3 (representing a >130 percent increase) was considered a positive response.

Forty-nine women (80 percent) had positive serum index values. Complete prenatal and delivery records were available for review in 29 of these women, and they formed the basis for the study. The fetuses were not evaluated systematically. Fetal hyperthyroidism was defined as persistent tachycardia (>160 beats/minute), goiter, or hydrops; high fetal serum free thyroxine (T_4) concentrations alone were not considered to indicate fetal hyperthyroidism. All the neonates were evaluated for hyperthyroidism, and given a diagnosis of hyperthyroidism if they had symptoms and signs of hyperthyroidism (tachycardia, goiter, irritability, hyperphagia, heart failure) and high serum free T_4 and low serum TSH concentrations.

Results The 29 women (mean age, 29 years; range, 18 to 40) had 35 singleton pregnancies ending with live births. During these 35 pregnancies; 11 of the women were treated with propylthiouracil; 8 women were treated with T_4, for radioiodine- or surgery-induced hypothyroidism; 6 received propylthiouracil and T_4; and the remainder received neither. The serum thyroid-stimulating immunoglobulin measurements were done during the second trimester in all the pregnancies. The index values ranged from 1.1 to 15.0 (extrapolated from Figure 1).

Cordocentesis was done in seven fetuses at 24 to 35 weeks of gestation; their mothers had index values ranging from 3.3 to 15.0. Four of the fetuses had high serum free T_4 concentrations. One had neonatal hyperthyroidism at birth a week later. The other three infants were normal at birth; the mothers of two had been taking propylthiouracil and were given a higher dose. Among the three fetuses with normal serum free T_4 concentrations, one had neonatal hyperthyroidism at birth three weeks later.

Overall, 29 of the 35 infants (83 percent) were delivered vaginally, and 6 (17 percent) by cesarean section. Nine infants (26 percent) were born preterm (<37 weeks), and 6 (17 percent) had intrauterine growth restriction. Six infants (17 percent) had neonatal hyperthyroidism, including two infants delivered by each of two mothers. Five of these 6 infants had tachycardia and 2 had heart failure; all were treated with propylthiouracil. The mothers' serum thyroid-stimulating immunoglobulin index values ranged from 5.8 to 15.0; one mother was taking T_4 and two were taking propylthiouracil. Among the 29 normal infants, the mothers of six (21 percent) had serum index values >5.0. The sensitivity and specificity of a serum index value ≥5 for predicting neonatal hyperthyroidism were 100 percent and 79 percent, respectively. The positive predictive value was 40 percent and the negative predictive value was 100 percent.

Conclusion Among pregnant women with hyperthyroidism caused by Graves' disease, only those with very high serum thyroid-stimulating immunoglobulin index values have fetuses and neonates at risk for hyperthyroidism.

COMMENTARY

Virtually all pregnant women who have hyperthyroidism have as its cause Graves' disease, whether the hyperthyroidism preceded or began during the pregnancy. Among these women, it is now clear, as reported by Peleg et al. and others (1), that only those who have very high serum concentrations of TSH receptor-stimulating antibodies are likely to have fetuses and neonates who have hyperthyroidism.

Should these antibodies be measured in all pregnant women with any history of Graves' disease at about 15 weeks of gestation, when the fetal thyroid is responsive to thyroid stimulators? That seems inappropriate, and could be misleading. The values are not often high, and even if they are, the fetus and neonate may not have hyperthyroidism. It seems more appropriate to monitor fetal growth, thyroid size, heart rate, and activity clinically and by ultrasonography. In the unlikely event there are unequivocal signs of fetal hyperthyroidism (poor fetal growth, goiter, hyperactivity), then—depending on the proximity to term—measure serum free T_4 and TSH in serum obtained by cordocentesis or very soon after delivery.

Robert D. Utiger, M.D.

Reference

1. Tamaki H, Amino N, Aozasa M, et al. Universal predictive criteria for neonatal overt thyrotoxicosis requiring treatment. Am J Perinatol 1988;5:152-8.

Patients with Graves' ophthalmopathy may have long-term impairment in vision and quality of life

Terwee C, Wakelkamp I, Tan S, Dekker F, Prummel MF, Wiersinga W. Long-term effects of Graves' ophthalmopathy on health-related quality of life. Eur J Endocrinol 2002;146:751-7.

SUMMARY

Background Patients with Graves' ophthalmopathy may have persistent changes in the appearance and function of their eyes, and these changes may lead to long-term psychological problems and limitations in physical and psychosocial activities. In this study the long-term effects of Graves' ophthalmopathy on general and visual quality of life and on visual function were assessed.

Methods The main study group consisted of patients with Graves' ophthalmopathy treated with external-beam radiation, prednisone, or both, at a referral center between 1982 and 1992; the patients were studied in 1999-2000. Other study groups were patients with Graves' ophthalmopathy studied at the time of radiation therapy or orbital surgery in 1997-1998, and subjects from the general population (results from the literature). The study subjects completed one or more of several questionnaires relating to quality of life, and the patients with ophthalmopathy also completed a Graves' ophthalmopathy quality-of-life questionnaire and were evaluated by an ophthalmologist.

Results The previously treated ophthalmopathy group consisted of 247 patients, of whom 34 (14 percent) had died, 45 (18 percent) declined to participate, and 168 (68 percent) were studied 7 to 23 years (median, 12) after therapy (Table 1). The patients studied while being treated were similar, except with respect to some eye findings.

Both groups of patients with ophthalmopathy scored lower than the normal subjects on several components of the general quality-of-life questionnaire, and the scores on the Graves' ophthalmopathy quality-of-life questionnaire were lower in the patients being treated than in those previously treated (Table 2).

In the previously treated patient group, those who were non-smokers had higher scores on the Graves' ophthalmopathymopathy quality-of-life score than smokers. Patients treated with radiation tended to score lower on the general quality-of-life questionnaires. Patients considered to have responded to radiation or prednisone therapy (decreased soft-tissue changes, proptosis, and diplopia; increased visual acuity) scored higher on both questionnaires.

Conclusion Patients with Graves' ophthalmopathy may have persistent impairment in the appearance and function of their eyes and a decreased quality of life.

Table 1. Characteristics of Patients with Graves' Ophthalmopathy.

	Treated Patients (n=168)	Patients Being Treated (n=206)
Age—yr (±SD)	58±13	50±12
Women/men (%)	78/22	83/17
Radiation/prednisone/both—(%)	13/32/55	5/29/16
Current eye findings	(n=154)	(n=206)
Soft tissue changes—no/yes (%)	87/13	16/84
Proptosis—≤19 mm/≥20 mm (%)	40/60	62/38
Diplopia—no/yes (%)	49/51	37/63
Visual acuity—normal/impaired (%)	72/28	78/22

Table 2. Scores on the General and Graves' Ophthalmopathy Quality-of-Life Questionnaires.

	Treated Patients (n=163)	Patients Being Treated (n=204)	Normal Subjects (n=750)
Mobility—good/poor (%)	61/39	66/34	95/5
Usual activities—yes/no	59/41	34/66	86/14
Pain/discomfort—no/yes (%)	42/58	30/70	68/32
Anxiety/depression—no/yes (%)	68/32	46/54	84/16
Visual function*	78±24	58±28	
Appearance of eyes*	77±22	58±25	

*Mean (±SD) score on scale of 0 to 100 (marked limitation or abnormality to no limitation or abnormality).

COMMENTARY

This study confirms that patients with Graves' ophthalmopathy severe enough to warrant glucocorticoid or orbital radiation are likely to have persistent visual deficits that adversely affect their quality of life.

As acknowledged by the authors, there are many difficulties with the interpretation of data from this study. Referral bias resulted in preselection of patients with more severe eye disease, limiting the applicability of the findings. The patients with Graves' ophthalmopathy were older and less educated than the reference population, both of which diminish general quality-of-life scores.

Several questions go unanswered. What were the quality-of-life scores in patients in whom eye appearance and function were restored to normal by glucocorticoid or radiation therapy? Are there lingering psychological effects associated with the illness and therapy apart from a persistent visual deficit or altered appearance?

Despite the limitations of the study, the authors found that both previously treated and currently treated patients with Graves' ophthalmopathy have lower quality-of-life scores than a reference population. Demonstration of an improvement in these important subjective changes may therefore become a useful measure of successful therapy.

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Germline loss-of-function mutations of the thyrotropin-receptor gene are a cause of subclinical hypothyroidism

Alberti L, Proverbio MC, Costagliola S, Romoli R, Boldrighini B, Vigone MC, Weber G, Chiumello G, Beck-Peccoz P, Persani L. Germline mutations of TSH receptor gene as cause of nonautoimmune subclinical hypothyroidism. J Clin Endocrinol Metab 2002;87:2549-55.

SUMMARY

Background Patients who have germline loss-of-function mutations in both alleles of the thyrotropin (TSH)-receptor gene may have either overt or subclinical hypothyroidism, and those who have a mutation in one allele may be normal or have subclinical hypothyroidism. In this study mutations of the TSH receptor were sought in patients with subclinical hypothyroidism who had no evidence of autoimmune thyroid disease.

Methods The study subjects were 10 patients (4 female and 6 male; age range, 23 days to 25 years) with subclinical hypothyroidism (initial serum TSH concentration, 6.6 to 46.0 mU/L, normal serum free thyroxine [T_4] concentrations) and their parents and siblings. All the patients had normal serum antithyroid peroxidase, antithyroglobulin, and anti-TSH receptor antibody concentrations. Three of the five patients who had been tested for hypothyroidism as neonates had high blood-spot TSH values. Ultrasonography revealed thyroid hypoplasia in two patients and a normal thyroid gland in eight patients.

DNA was extracted from peripheral blood leukocytes, and the entire coding sequence and exon-intron boundaries of the TSH-receptor gene were sequenced (the receptor is composed of an N-terminal extracellular domain, a transmembrane domain, and a C-terminal intracellular domain). The DNA substitutions found in the patients were introduced into the wild-type TSH-receptor gene by site-directed mutagenesis. Wild-type and mutated DNA was inserted into cells and the cells were cultured for 48 hours. Intact cells and cells rendered permeable to antibodies then were examined by flow cytometry using anti-TSH receptor antibodies. In addition, cyclic AMP production was measured in transfected cells incubated without and with bovine TSH.

Results Five different mutations in the TSH-receptor gene were detected in 4 of the 10 patients. One patient (age 25 years) was a compound heterozygote, with a mutation in the extracellular domain of the receptor in one allele of the gene and a mutation in the transmembrane domain in the other allele (serum TSH concentrations, 31.5 to 46.0 mU/L). The parents and brother of this patient had one mutated and one wild-type allele, and each had normal or slightly high serum TSH concentrations on different occasions (3.5 to 6.2 mU/L). The other three patients (aged 23 days, 30 days, and 5 years) were heterozygotes, with one wild-type allele and a mutation in either the extracellular domain or the transmembrane domain of the other allele. A parent or sibling of two of these three patients carried the same allele (and had slightly high serum TSH concentrations). The third patient had a normal mother and sibling; her father was not tested.

Similar quantities of TSH receptors were detected in permeabilized cells transfected with wild-type and mutant TSH-receptor DNA, but fewer TSH receptors were detected on intact cells transfected with mutant DNA as compared with cells transfected with wild-type DNA. These results indicate that the cells synthesized similar amounts of TSH receptors, but the mutated receptors were not inserted into the cell membrane. As compared with cells transfected with wild-type TSH-receptor DNA, cells transfected with mutant DNA produced little cyclic AMP, both basally and in response to TSH.

Serum TSH concentrations were high (6.1 to 26.7 mU/L) in a parent and one or more siblings of four of the six patients in whom no mutation was detected.

Conclusion Germline loss-of-function mutations in one or both alleles of the TSH-receptor gene can cause subclinical hypothyroidism.

COMMENTARY

These results document that the presence of one normal allele of the TSH-receptor gene does not necessarily provide thyroid cells with enough receptors to allow normal thyroid secretion.

The results also raise the possibility that genetic disorders may be a cause of subclinical hypothyroidism in the general population, not just in infants with congenital hypothyroidism. In most patients subclinical hypothyroidism is attributed to chronic autoimmune thyroiditis, which seems reasonable enough in patients with high serum antithyroid antibody concentrations. But what about those in whom the serum antibody concentrations are not high? Might not some of them have a mutation reducing TSH receptors or a step in intracellular TSH signaling? As a first step in investigating this possibility, serum TSH could be measured in parents, siblings, and offspring of a group of adults with subclinical hypothyroidism.

Robert D. Utiger, M.D.

Progression from subclinical to overt hypothyroidism is most likely in women with higher serum TSH concentrations and high serum antithyroid antibody titers

Huber G, Staub J-J, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab 2002;87:3221-6.

SUMMARY

Background Subclinical hypothyroidism (high serum thyrotropin [TSH] and normal serum thyroid hormone concentrations) is common, and some patients later have overt hypothyroidism. This study was undertaken to determine the rate of progression of subclinical hypothyroidism to overt hypothyroidism (high serum TSH and low serum free thyroxine [T_4] concentrations) and to identify the risk factors for progression.

Methods The study subjects were 82 women (mean age, 51 years) with subclinical hypothyroidism on two occasions one month apart. They included 42 women with a history of hyperthyroidism caused by Graves' disease, of whom 32 had been treated with radioiodine 1 to 28 years earlier (median, 7) and 10 by surgery; 29 women with chronic autoimmune thyroiditis; and 11 with nontoxic goiter, all previously treated by surgery. The women were evaluated by clinical examination, including assessment of hypothyroid symptoms by two scoring systems (Billewicz, Zulewski), and measurements of serum TSH, free T_4, antithyroid microsomal (peroxidase) antibodies, lipids, and creatine kinase at yearly intervals. The study end points were overt hypothyroidism on two occasions (interval not stated), or initiation of T_4 therapy for Graves' ophthalmopathy, prevention of recurrent goiter after thyroidectomy, depression, hypercholesterolemia, or infertility.

Results The mean follow-up period was 9 years (range, 0.5 to 26), during which there were no changes in mean symptom scores, serum lipid or creatine kinase concentrations, or serum free T_4 concentrations, whereas the mean (±SE) serum TSH concentration increased from 12.0±1.1 to 18.9±2.7 mU/L. At base line, 21 women (26 percent) had serum TSH concentrations >4.0 to 6.0 mU/L, 36 women (44 percent) had values of >6 to 12 mU/L, and 25 women (30 percent) had values of >12 mU/L. The mean base-line and final serum TSH concentrations in these three groups were, respectively, 5.0 and 6.0 mU/L, 8.6 and 15.9 mU/L, and 22.9 and 34.1 mU/L. The base-line and final values for the symptom scores and other measurements, including serum free T_4 concentrations, were similar in all three subgroups, as they were in all 82 women.

During follow-up 23 women (28 percent) developed overt hypothyroidism, 56 (68 percent) had persistent subclinical hypothyroidism, and 3 (4 percent) became euthyroid. The likelihood of overt hypothyroidism increased as a function of the base-line serum TSH concentration; as determined by Kaplan-Meier analysis, the 10-year risk was 0 percent in the women with base-line serum TSH concentrations >4 to 6 mU/L, 43 percent (3 percent/year) in the women with base-line concentrations >6 to 12 mU/L, and 77 percent (11 percent/year) in the women with base-line concentrations >12 mU/L. Among the 56 women who had persistent subclinical hypothyroidism, 17 (30 percent) were treated with T_4, and they were then excluded from further follow-up.

A high serum antithyroid microsomal antibody titer at base line was an additional risk factor for overt hypothyroidism. The cumulative incidence of overt hypothyroidism was 23 percent among the 40 women with normal serum antibody titers and 58 percent among the 42 women with high serum antibody titers.

The likelihood of overt hypothyroidism was similar in the 32 women who had Graves' hyperthyroidism and had been treated with radioiodine and the 29 women with chronic autoimmune thyroiditis.

Conclusion Among women with subclinical hypothyroidism the risk of overt hypothyroidism is higher in those with higher serum TSH concentrations and high serum antithyroid microsomal antibody titers.

COMMENTARY

Whether people with subclinical hypothyroidism should be treated with T_4 is controversial. One argument for treatment is to prevent progression to overt hypothyroidism, but how often does that occur and can it be predicted? The answers from both this and other studies is that it does occur, and that it can to some extent be predicted. Some of the studies, like this one, were of people known to have thyroid disease, but others, like the 20-year Whickham, United Kingdom study, were community-based (1).

Robert D. Utiger, M.D.

Reference

1. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995;43:55-68.

Serum concentrations of multiple enzymes may be high in patients with hypothyroidism

Saha B, Maity C. Alteration of serum enzymes in primary hypothyroidism. Clin Chem Lab Med 2002;40:609-11.

SUMMARY

Background Some patients with primary hypothyroidism have high serum concentrations of creatine kinase, aspartate aminotransferase, and other enzymes, but the relationships between the elevations and the severity of hypothyroidism, as determined by measurements of serum thyrotropin (TSH), are not clear. In this study these and other enzymes were measured and the results correlated with serum thyrotropin (TSH) concentrations in a large group of patients with primary hypothyroidism.

Methods The study subjects were 114 patients, aged 7 to 65 years, with spontaneously occurring primary hypothyroidism, with or without thyroid enlargement, as defined by a serum TSH concentration >14 mU/L; serum thyroxine was not measured. Patients with a history of other thyroid diseases or treatment for thyroid disease, other illnesses, or treatment with any drug that affects thyroid function, and pregnant women were excluded. Fasting blood samples were collected before and 3 weeks to 11 months after the initiation of thyroxine therapy for measurements of serum TSH, creatine kinase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and amylase. No age- and sex-matched normal subjects were studied at the same time.

Results Forty-seven of the 114 patients (41 percent) had normal serum concentrations of all five enzymes. Among the other patients, 8 (7 percent) had high serum concentrations of creatine kinase, aspartate aminotransferase, alanine aminotransferase, and amylase, and the remainder had high serum concentrations of one to three of these enzymes. Among the individual enzymes, high values were found in from 3 percent to 37 percent of the patients (Table).

Table. Serum Enzyme Concentrations in Patients with Hypothyroidism

	Creatine Kinase	Aspartate Amino-transferase	Alanine Amino-transferase	Amylase	Alkaline Phosphatase
Patients with high values	42 (37%)	40 (35%)	33 (29%)	17 (15%)	3 (3%)

Fifty-three patients had serum TSH concentrations <100 mU/L, of whom 38 (72 percent) had normal serum concentrations of all five enzymes. In this group there was no correlation between serum TSH concentrations and the serum concentrations of any of the enzymes.

Serum creatine kinase concentrations decreased from high to normal or decreased within the normal range during thyroxine therapy. The patterns of change in the other enzymes were similar.

Conclusions Among several serum enzymes, the concentrations of creatine kinase are most often high in patients with hypothyroidism, but there is little correlation between serum enzyme and TSH concentrations.

COMMENTARY

The serum enzymes measured in these patients with hypothyroidism originate in different tissues, and they may be cleared from the circulation by different tissues as well. In the case of creatine kinase, the increases are in the MM isoenzyme that predominates in skeletal muscle, and the high serum concentrations are caused by the increased permeability of skeletal muscle cells, but it is likely that clearance of the enzyme is slowed as well. A combination of increased release from tissues as diverse as the liver, pancreas, salivary glands, and skeleton, and slowed clearance probably explains the increased serum concentrations of the other enzymes as well. Physicians who order serum enzyme measurements should be aware that hypothyroidism can cause elevations not only of serum creatine kinase but also other enzymes.

High serum creatine kinase concentrations occur not only in patients with overt hypothyroidism, but also in those with subclinical hypothyroidism. In a study of 104 patients with widely varying serum TSH concentrations serum creatine kinase (and myoglobin) and TSH concentrations were positively correlated, and the mean serum creatine kinase concentration in the patients with overt hypothyroidism was seven times that in the normal subjects (579 versus 86 U/L) (1). The relationship between muscle dysfunction and serum creatine kinase concentrations in patients with hypothyroidism varies. Patients with myopathy usually have high concentrations (2), and massive elevations have been found in a few patients, for example to 29,160 U/L in a man with marked proximal myopathy that responded well to thyroxine therapy (3). Other patients with high serum creatine kinase concentrations do not have overt myopathy, but it probably isn't looked for very diligently.

Robert D. Utiger, M.D.

References

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2. Rodolico C, Toscano A, Benvenga S, et al. Myopathy as the persistently isolated symptomatology of primary autoimmune hypothyroidism. Thyroid 1998;8:1033-8.

3. Scott KR, Simmons Z, Boyer PJ. Hypothyroid myopathy with a strikingly elevated serum creatine kinase level. Muscle Nerve 2002;26:141-4.

Thyroxine inhibits thyrotropin secretion in patients with central hypothyroidism

Shimon I, Cohen O, Lubetsky A, Olchovsky D. Thyrotropin suppression by thyroid hormone replacement is correlated with thyroxine level normalization in central hypothyroidism. Thyroid 2002;12:823-7.

SUMMARY

Background Patients with central hypothyroidism typically have normal or low serum thyrotropin (TSH) concentrations and low serum thyroxine (T_4) concentrations. The efficacy of treatment with T_4 in these patients is usually assessed by measurements of serum free T_4, and there has been little study of the relationship between their serum TSH and free T_4 concentrations before and during T_4 treatment. This retrospective study was undertaken to evaluate this relationship, with the hypothesis that TSH secretion in these patients is sensitive to changes in serum free T_4 concentrations, but is lower at all serum free T_4 concentrations than it is in normal subjects or patients with primary hypothyroidism.

Methods The study subjects were 41 patients (17 women, 24 men; mean age, 48 years [range, 16 to 77]). All had adult-onset hypothalamic-pituitary disease and low serum free T_4 concentrations; their serum TSH concentrations were low, normal, or slightly high. The hypothalamic-pituitary diseases were: nonsecreting pituitary adenoma, 16 patients; somatotroph adenoma, 6 patients; prolactinoma, 5 patients; and craniopharyngioma, pituitary apoplexy, histiocytosis X, hypophysitis, sellar cyst, meningioma, and empty sella, 3 or fewer patients each. Thirty patients had been treated surgically, and 18 had received radiation therapy. Thirty-three patients were taking glucocorticoids, 22 estrogen or testosterone, and 9 vasopressin.

The patients were treated with 50 to 150 μg of T_4 daily (mean, 1.15 μg/kg/day). The initial dose was increased in increments of 25 μg until the patient was clinically euthyroid and had a normal serum free T_4 concentration (interval between dose changes not given). Serum free T_4 and TSH (assay sensitivity, 0.005 mU/L) were measured at multiple times in each patient during a mean follow-up period of 7 years (range, 0.5 to 23). The results in 20 patients who had at least three consecutive measurements before and during treatment were compared with similarly obtained results in 17 patients with primary hypothyroidism.

Results The mean (±SE) pretreatment serum TSH concentration in the patients with central hypothyroidism was 2.0±0.2 mU/L (range, 0.06 to 5.8); five patients had values >4.0 mU/L, and 9 had values <0.5 mU/L. The changes in serum TSH and free and total T_4 concentrations during treatment are shown in the Table.

Table. Serum TSH and Thyroid Hormone Concentrations in Patients with Central Hypothyroidism during T_4 Treatment.

	Base Line	6 Months	28 Months	Last
T_4 dose (μg/day)	0	58±5	81±5	86±6
Serum TSH (mU/L)	2.0±0.2	1.0±0.2	0.6±0.2	0.5±0.2
Serum free T_4 (ng/dL)*	0.6±0.04	0.9±0.1	1.1±0.1	1.2±0.1
Serum T_4 (μg/dL)*	4.4±0.2			8.1±0.4

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

During treatment, 92 percent of patients who had serum TSH concentrations <0.1 mU/L had normal serum free T_4 concentrations, as compared with only 34 percent of patients who had serum TSH concentrations >1 mU/L.

The mean pretreatment serum TSH concentration in the patients with primary hypothyroidism was 75.5±19.6 mU/L, and the final concentration was 5.4±2.2 mU/L. The slopes of the regression lines for the logarithm of the serum TSH concentrations as a function of the serum free T_4 concentrations before and during treatment in the 20 patients with central hypothyroidism and 17 patients with primary hypothyroidism were parallel, but at a zero serum free T_4 concentration the serum TSH concentration was approximately three log units lower in the patients with central hypothyroidism.

Conclusion Serum TSH concentrations vary inversely with serum free T_4 concentrations in patients with central hypothyroidism, indicating that T_4-mediated negative feedback is preserved, but at a considerably lower set point than in patients with primary hypothyroidism.

COMMENTARY

Shimon et al. have clearly demonstrated that TSH secretion in patients with central hypothyroidism is sensitive to changes in serum free T_4 concentrations, albeit in a quantitatively abnormal way. The set point of TSH secretion is lowered. As compared with normal subjects, not only is the patients' TSH secretion low relative to the ambient serum free T_4 concentration, but also it is much more easily inhibited by small increases in serum free T_4 concentrations. While relatively normal serum TSH concentrations in patients with central hypothyroidism being treated with T_4 suggest that treatment was inadequate, the slopes of the serum TSH-free T_4 plots were different in different patients, so that it is doubtful that measurements of serum TSH, even if done using a very sensitive assay, can supplant measurements of serum free T_4 as an indicator of the adequacy of treatment in patients with central hypothyroidism.

Robert D. Utiger, M.D.

Thyroxine therapy does not reduce the size of benign solitary thyroid nodules: systematic analysis of multiple studies

Castro MR, Caraballo PJ, Morris JC. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: a meta-analysis. J Clin Endocrinol Metab 2002;87:4154-9.

SUMMARY

Background Patients with a benign solitary thyroid nodule are often treated with thyroxine (T_4) to reduce nodule size, but the efficacy of this therapy is uncertain. This study was a meta-analysis of controlled clinical trials of T_4 therapy in patients with benign solitary thyroid nodules.

Methods The literature was searched to identify trials of T_4 therapy in patients with a thyroid nodule. To be included in the analysis, the trial had to be a randomized controlled trial of patients with a single thyroid nodule, as detected by palpation, proven to be benign by fine-needle aspiration biopsy. Other inclusion criteria were measurements of nodule volume by ultrasonography, with a response to therapy being defined as a >50 percent decrease in volume; documentation of suppression of thyrotropin (TSH) secretion by T_4; and duration of treatment of at least six months.

Results Thirteen trials of T_4 therapy in patients with a benign solitary thyroid nodule were identified. Among them, six met the inclusion criteria and were therefore included in the meta-analysis. One of the excluded trials described the same patients after treatment for five years; the others were excluded because they did not meet the inclusion criteria in one or more ways.

The six trials included 346 patients (313 women, 33 men), all of whom had normal thyroid function. The mean age ranged from 34 to 48 years. Most trials included only patients with a solid nodule or a nodule that was ≤20 percent cystic. At base line, the patients in the T_4-treatment and control groups in each study were well matched in clinical characteristics, thyroid-function test results, and nodule volume. The mean nodule volumes in individual studies varied considerably, from 3.0 and 2.6 mL in the T_4-treatment and control groups, respectively, in study 1 (Table) to 16.4 and 13.6 mL in the respective groups in study 5. The duration of treatment varied from 6 to 12 months. The doses of T_4 ranged from 1.5 to 3 μg/kg; in some studies the dose was fixed, but in others it was adjusted to meet a specific serum TSH target, usually just below the lower limit of the normal range. The control group received a placebo in four trials and nothing in two. The investigators who measured nodule volume were not aware of treatment-group assignment in all trials.

Overall, nodule volume decreased by more than 50 percent in 22 percent of the T_4-treated patients and by 10 percent in the control patients; in only one trial was the difference statistically significant. The relative risk (likelihood) of a >50 percent decrease in nodule volume in the T_4-treatment group, as compared with the control group, is shown in the Table. The mean nodule volume was similar in the T_4-treatment and control groups at the end of each trial, except trial 4.

Table. Relative Risk (Likelihood) of a >50 Percent Decrease in Nodule Volume during T_4 Treatment.

Trial	No. of Patients	Location	Relative Risk (95% Confidence Interval)
1	53	USA	0.7 (0.2-2.4)
2	40	Spain	1.3 (0.3-5.2)
3	101	Italy	3.3 (1.0-11.2)
4	45	Italy	18.2 (1.1-295.2)
5	45	Brazil	3.4 (0.8-15.2)
6	62	Iran	1.4 (0.4-4.5)
Total	346		1.9 (1.0-3.8)

Conclusion In patients with a benign solitary thyroid nodule, T_4 therapy for 6 to 12 months does not result in a substantial decrease in nodule size.

COMMENTARY

The results of this meta-analysis of T_4 treatment in patients with a benign solitary nodule were similar to those of a preceding one (1). The first meta-analysis included seven trials (413 patients); nodule volume decreased by >50 percent in 26 percent of the T_4-treated patients and 12 percent of the control patients ($P<0.05$). Five of these trials were included in this new analysis, two were excluded because they were not randomized, and one new trial was included. These trials were heterogeneous, in that nodule size, cystic content of the nodules, and dose of T_4 varied. The pathology of the nodules and their content of TSH receptors, presumably a key determinant of the efficacy of T_4 therapy, surely varied too.

Even if T_4 therapy does not decrease nodule size, it might prevent nodule growth. Summary data on this point can be found in reference 1; in four trials (trials 1, 3, 4, and 5) nodule volume increased by >50 percent in 8 percent of the T_4-treated patients and 17 percent of the control patients ($P<0.05$).

Any continued use of T_4 in these patients rests primarily on the lack of simple alternative treatments. Thyroid nodules can be destroyed by injections of ethanol, but the treatment is not simple. As for T_4 therapy, the benefit, if any, is so marginal, and the hazards, however small, of the subclinical hyperthyroidism that results from the therapy are such that doing nothing seems wiser.

Robert D. Utiger, M.D.

Reference

1. Zelmanovitz F, Genro S, Gross JL. Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analysis. J Clin Endocrinol Metab 1998;83:3881-5.

Completion thyroidectomy can be done safely after thyroid lobectomy in patients with thyroid carcinoma

Kupferman ME, Mandel SJ, DiDonato L, Wolf P, Weber RS. Safety of completion thyroidectomy following unilateral lobectomy for well-differentiated thyroid cancer. Laryngoscope 2002;112:1209-12.

SUMMARY

Background Patients with a thyroid nodule in whom a biopsy reveals a follicular tumor or is nondiagnostic are often treated by unilateral thyroid lobectomy. If the nodule proves to be a follicular or papillary carcinoma, the patients are usually advised to undergo contralateral thyroid lobectomy—so-called completion thyroidectomy. One rationale for completion thyroidectomy is that the remaining lobe may contain one or more microscopic thyroid carcinomas. Another is that it is difficult to destroy a normal thyroid lobe with radioiodine (I-131), and the presence of normal thyroid tissue reduces the value of measurements of serum thyroglobulin as a tumor maker and makes it difficult if not impossible to treat recurrent tumor with I-131. This retrospective case study was done to determine the safety of completion thyroidectomy.

Methods The study subjects were all 36 patients who underwent thyroid lobectomy and then completion thyroidectomy by one surgeon between 1997 and 2000. There were 32 women and 4 men; mean age, 44 years (range, 19 to 59). The completion operation was performed via a low-collar incision, with excision of the scar from the previous thyroid lobectomy. Parathyroid and laryngeal- nerve function were routinely assessed pre- and postoperatively.

Results All patients underwent fine-needle aspiration biopsy before their initial operation. The biopsy diagnoses were follicular tumor in 32 patients (89 percent) and Hurthle-cell tumor in 1 patient (3 percent); the biopsy was nondiagnostic in 3 patients (8 percent). The findings at the initial thyroid lobectomy were follicular variant of papillary carcinoma in 29 patients (80 percent), follicular carcinoma in 6 patients (17 percent), and Hurthle-cell carcinoma in 1 patient (3 percent). Two patients (6 percent) had transient hypocalcemia postoperatively.

Completion thyroidectomy, done between 2 and 103 days (mean, 43) after the initial thyroid lobectomy, revealed thyroid carcinoma in 20 of the 36 patients (56 percent). The pathological diagnosis was follicular variant of papillary carcinoma in 18 patients (50 percent), follicular carcinoma in 1 patient (3 percent), and Hurthle-cell carcinoma in 1 patient (3 percent). No tumor was found in 16 patients (44 percent). Five patients (14 percent) had transient hypocalcemia, but none had permanent hypocalcemia. No patient had recurrent laryngeal-nerve injury, as assessed by nasopharyngolaryngoscopy, after the initial or completion thyroidectomy.

Conclusion In patients with thyroid nodules that prove at surgery to be thyroid carcinomas, completion thyroidectomy can be performed safely a few days or many weeks after initial surgery and reveals thyroid carcinoma in approximately 50 percent of patients.

COMMENTARY

The need for completion thyroidectomy in patients who present with a thyroid nodule is based not only on the limitations of fine-needle-aspiration biopsy and frozen-section diagnosis at the time of surgery, but also on the patient's or surgeon's hope that the nodule will prove to be benign, obviating the need for removal of the contralateral lobe of the thyroid and therefore the need for lifelong thyroxine therapy. This hope is sustained by the fact that the majority of patients in whom biopsy reveals a follicular or Hurthle-cell tumor do not have a follicular or Hurthle-cell carcinoma. In them, unilateral thyroid lobectomy is adequate treatment. In patients in whom the nodule proves to be a carcinoma on examination of permanent microscopic sections, a recommendation for completion thyroidectomy is based on the belief that bilateral thyroid lobectomy (usually near-total thyroidectomy) is a more effective treatment for papillary or follicular thyroid carcinoma than is a unilateral lobectomy. This belief is based on the fact that the contralateral lobe often contains one or more foci of carcinoma, as was the case in 56 percent of the patients in this study, and that some of these foci are clinically important, based on the results of studies demonstrating the superiority of near-total thyroidectomy over unilateral lobectomy as treatment for thyroid carcinoma (see page 53).

The question of the optimal timing of completion thyroidectomy was not addressed in this study, but in a recent study of 100 consecutive patients undergoing this operation, the frequency of postoperative complications was low, and not related to the timing of the completion operation (1).

Robert D. Utiger, M.D.

Reference

1. Tan MP, Agarwal G, Reeve TS, et al. Impact of timing on completion thyroidectomy for thyroid cancer. Br J Surg 2002;89:802-4.

Changes in surgical practice and use of postoperative radioiodine therapy have had limited effect on outcome in patients with papillary thyroid carcinoma

Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, Maurer MS, McIver B, Mullan BP, Oberg AL, Powell CC, van Heerden JA, Goellner JR. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg 2002;26:879-85.

SUMMARY

Background There has been continued debate regarding the most appropriate surgical treatment and the value of postoperative radioiodine (I-131) therapy for patients with papillary thyroid carcinoma. This study determined the temporal trends in therapy and the cause-specific mortality and tumor recurrence rates in a large cohort of patients with papillary carcinoma.

Methods The study subjects were all 2444 patients (1648 females, 796 males; median age, 46 years [range, 4 to 90]) with papillary carcinoma who underwent surgery at the Mayo Clinic from 1940 to 1999. The median follow-up was 15 years (longest, 60 years). Among the 2444 patients, 2305 (94 percent) were considered cured, because resection was thought to be complete or no metastases were detected within 30 days after surgery.

Results The mean tumor size was 2.1 cm (range, 0.1 to 15.0). At surgery, 693 patients (28 percent) had multicentric tumors, 328 patients (13 percent) had locally invasive tumors, and 983 patients (40 percent) had regional lymph node metastases. Based on the MACIS scoring system (distant Metastases [0, 3], Age [3.1 if age ≤39 years, 0.08 × age if older], Completeness of resection [0, 1], local invasion [0, 1], and tumor Size [0.3 × tumor size], 2038 patients (83 percent) were considered low risk (score, <6) and 406 (17 percent) were high risk (score, ≥6).

The initial operation was a near-total or total thyroidectomy in 1905 patients (78 percent), bilateral subtotal lobectomy in 215 patients (9 percent), unilateral lobectomy in 284 patients (12 percent); the remainder had lesser operations. Postoperatively, 774 patients (33 percent) received I-131 therapy for remnant destruction. I-131 was not given during the 1940s; the rates in subsequent decades are shown in the Table. Risk status was not a determinant of I-131 therapy; for example, in the 1980s, 57 percent of low-risk patients and 50 percent of high-risk patients received I-131, and in the 1990s the respective percentages were 42 percent and 49 percent.

Among the 2305 patients thought to have compete resections, 673 (29 percent) died, a rate similar to that expected for people living in the same region. The cancer-specific mortality rates were 4 percent at 10 years and 5 percent at 15, 20 and 25 years. The tumor recurrence rates at these times were 11, 12, 13, and 14 percent, respectively. The 10-year cancer-specific mortality and recurrence rates by decade are shown in the Table.

Table. Rates of Bilateral Surgery, I-131 Therapy, Cancer-Specific Mortality, and Tumor Recurrence in 2305 Patients with Papillary Carcinoma, by Decade.

	Decade of Diagnosis					
	1940-49	1950-59	1960-69	1970-79	1980-89	1990-99
Bilateral surgery (%)*	30	78	94	97	96	91
I-131 therapy (%)*	0	4	2	18	57	46
Mortality—10-yr (%)	7	4	6	3	2	2
Recurrence—10-yr (%)	18	9	8	10	8	10

*Extrapolated in part from Figure 2 of article.

Despite the differences in extent of surgery and frequency of I-131 therapy, the 10-year cancer-specific mortality and recurrence rates did not vary in either the low-risk or high-risk patients during the five decades from 1950 to 1999.

Conclusion Among patients with papillary thyroid carcinoma, cancer-specific death rates and recurrence rates have changed little since 1950, despite the increasing extent of surgery and the increasing frequency of postoperative I-131 therapy.

COMMENTARY

There has been a long-running debate about the value of postoperative treatment with I-131 for the purpose of destroying any thyroid tissue remaining after surgery in patients with papillary carcinoma (remnant ablation). The main reason the debate continues is that all the studies of this treatment have been retrospective and observational, with inherent biases, especially selection bias.

In some studies, remnant ablation was associated with decreased mortality and recurrence rates in patients with all but the smallest tumors. In contrast, in this study by Hay et al. remnant ablation had little effect on mortality or recurrence rates in both low-risk and high-risk patients. However, the results may not be as compelling as they seem. Many of the results are given as percentages, and often the numbers of patients on whom these percentages are based are not given. This is particularly a problem with respect to the long-term follow-up results; the number of patients treated in the 1980s and 1990s and followed up for 10 or more years is likely to be small. Nonetheless, the results provide a strong argument for reconsidering the use of remnant ablation, especially in low-risk patients.

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

Hyer S, Vini L, O'Connell M, Pratt B, Harmer C. Testicular dose and fertility in men following I^{131} therapy for thyroid cancer. Clin Endocrinol 2002;56:755-8.

SUMMARY

Background Some men with thyroid carcinoma have transient decreases in spermatogenesis after radioiodine (I-131) therapy, but whether long-term fertility is reduced is not known. In this study the fertility of men with papillary or follicular thyroid carcinoma treated with varying doses of I-131 was determined, and radiation doses to the testes and serum follicle-stimulating hormone (FSH) concentrations were measured serially after I-131 therapy in subgroups of the men.

Methods The study subjects were 122 men with thyroid carcinoma who were less than 40 years old (median, 35; range, 23 to 39) when treated between 1949 and 1997; older men were excluded because most had completed their families. In 97 men the disease was limited to the thyroid, 22 had lymph node involvement, and 3 had metastases. All were treated surgically; 78 men then received 81 mCi (3 GBq) of I-131 to destroy remaining normal thyroid tissue, and 44 men received 230 to 1280 mCi (8.5 to 47.3 GBq) of I-131 for that purpose and to treat persistent, recurrent, or metastatic disease.

Information about fertility was obtained from the men at the time of follow-up visits or by mail. The men were asked if they had all the children they wished to have, and if they had not had children whether this was by choice. The radiation dose to each testis was measured by placement of a small thermoluminescent detector on the scrotum in 14 men. Serum FSH was measured before and at 1, 3, 6, 9, and 12 months after I-131 therapy in 14 men.

Results Among the 122 men, 29 had died or were lost to follow-up (median follow-up period, 21 years; range, 3 to 39). Among the remaining 93 men, 34 (37 percent) had not wished to have children, including three men who initially wished to have children but changed their minds because of the perceived risk of congenital anomalies in any offspring. The remaining 59 men (63 percent) had fathered 106 children 3.5 to 18 years after I-131 therapy. These 59 men included 12 men who received a single 81 mCi (3 GBq) dose of I-131 and had fathered 20 children, 19 men who received >81 to <380 mCi (3 to 14 GBq) and had fathered 36 children, and 28 men who received 380 to 1190 mCi (14 to 44 GBq) and had fathered 50 children. The interval between the last dose and fathering is not stated. None of the children had any major malformation.

The estimated mean radiation doses to each testis ranged from 6.4 cGy (64 rad) in seven men treated once with 81 mCi (3 GBq) of I-131 to 21.2 cGy (212 rad) in seven men treated two or more times with cumulative doses of 150 mCi (5.5 GBq) to 250 mCi (9.2 GBq) of I-131.

In seven men given 81 mCi (3 GBq) of I-131, serum FSH concentrations increased twofold or threefold one month after treatment, and returned to base line by 9 months. In seven other men who received two doses of I-131, serum FSH concentrations increased slightly more after the second dose than after the first dose, and returned to base line by 12 months. Two men had small transient increases in serum luteinizing hormone concentrations after therapy, but no change in serum testosterone concentrations.

Conclusion I-131 therapy does not reduce fertility in men with thyroid carcinoma.

COMMENTARY

The largest previous studies of the effects of I-131 therapy in men with thyroid carcinoma contained more detailed hormonal analyses in more men, with similar results—a rise and fall in serum FSH concentrations and little change in serum LH and testosterone concentrations (1,2). The fact that serum FSH concentrations rise transiently after single doses of I-131—and are persistently high in some men after repeated doses (1)—is strong evidence that I-131 can reduce spermatogenesis, although there have been no systematic studies of sperm production in these men. In one study, 11 men had fathered children, and single semen analyses in eight men revealed decreased numbers of motile sperm (1).

Hyer at al. found that men with thyroid carcinoma who have been treated with I-131 are fertile, but they may not be normally fertile. No man who wanted to father a child was unable to do so, but the men apparently were not asked whether the fathering took longer than expected or if they wished to have more children. And we do not know what the men had been told about fertility at the time of treatment, which may well have influenced their later desire not to have children. Nonetheless, given the available information, men who are to be treated with I-131 can be told that they should be fertile in the long term, unless they are treated repeatedly, but their fertility may be impaired in the first months after I-131 therapy.

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High serum antithyroglobulin concentrations after initial therapy are associated with recurrence in patients with thyroid carcinoma

Chung JK, Park YJ, Kim TY, So Y, Kim SK, Park DJ, Less DS, Lee MC, Cho BY. Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. Clin Endocrinol 2002;57:215-21.

SUMMARY

Background Some patients with differentiated thyroid carcinoma have high serum antithyroglobulin antibody concentrations not only before but also after surgical and radioiodine therapy, and persistently high values may be associated with recurrence of carcinoma. This study was done to determine the relationship between high serum antithyroglobulin antibody concentrations after initial treatment and outcome in patients with thyroid carcinoma.

Methods The study subjects were 226 patients with differentiated thyroid carcinoma treated by surgery and radioiodine who subsequently had no detectable thyroid remnants and serum thyroglobulin concentrations <1 ng/mL (independent of their serum thyrotropin concentrations at that time). Serum antithyroglobulin antibodies were measured then and during subsequent follow up in each patient, and the patients were evaluated for recurrence by imaging procedures or surgery. Serum thyroglobulin was measured by an immunoradiometric assay (sensitivity, <0.8 ng/mL; recovery of thyroglobulin, 93 to 133 percent), and serum antithyroglobulin antibodies were measured by a radioimmunoassay (values <100 U/mL were considered negative). Autoimmune thyroid disease was diagnosed by histology at initial surgery.

Results The initial serum antithyroglobulin antibody concentrations were <100 U/mL in 175 patients (77 percent), of whom 6 patients (3 percent) had a recurrence during follow-up (duration of follow-up not given) (Table). Serum antithyroglobulin concentrations were ≥100 U/mL in 51 patients (23 percent), of whom 25 (49 percent) had a recurrence after a mean (±SD) disease-free interval of 52±56 months, and 26 (51 percent) had no recurrence during a mean follow-up period of 25±13 months. Among the 31 patients who had recurrences, 4 had local recurrences, 21 had lymph node metastases, and 6 had lung or bone metastases.

Table. Clinical Characteristics of Patients with Thyroid Carcinoma with Low (Negative) and High Serum Antithyroglobulin Antibody Concentrations.

	Serum Antithyroglobulin <100 U/mL (n=175)	Serum Antithyroglobulin ≥100 U/mL (n=51)
Age (mean [±SD] yr)	44±13	44±13
Women/men	158/17	46/5
Histology (papillary/follicular)	163/12	51/0
Time after radioiodine therapy (mean [±SD] yrs)	3.3±3.7	3.5±4.2
Recurrence	6 (3%)	25 (49%)
Autoimmune thyroid disease	14 (8%)	16 (31%)

In the 51 patients with high serum antithyroglobulin antibody concentrations, the initial values were higher in the 25 patients who had a recurrence than in the 26 patients who did not (1124±1879 vs. 520±724 U/mL). Fourteen of these 25 patients responded to surgical or radioiodine therapy; serum antithyroglobulin antibody concentrations decreased in 10 and did not change or increased in 4. Serum antithyroglobulin antibody concentrations decreased in 19 of the 26 patients (73 percent) (to values <100 U/mL in 12 patients) who did not have a recurrence during follow-up; the values did not change in 3 patients and increased progressively in 4 patients.

Conclusion Patients with differentiated thyroid carcinoma who have high serum antithyroglobulin antibody concentrations after surgical and radioiodine therapy are more likely to have recurrent carcinoma than those with low concentrations.

COMMENTARY

Patients were selected for this study if they had very low serum thyroglobulin concentrations several years after surgery and administration of radioiodine for thyroid remnant destruction. The presence of high serum antithyroglobulin antibody concentrations at that time in 23 percent of the patients, however, implies that that some thyroglobulin was (or had recently been) present. If so, it was probably being produced by residual microscopic foci of thyroid carcinoma cells rather than normal thyroid cells. If this hypothesis is correct, then it is not surprising that patients with high serum antithyroglobulin antibody concentrations are likely to have clinically evident recurrences at some later time; indeed, it is surprising that the recurrence rate in this group was not higher. And of course it might be as the patients are followed longer; note that the patients who did not have a recurrence were followed for only about half as long as those who had a recurrence (25 vs. 52 months). Conversely, in patients with no remaining thyroid tissue at all, serum antithyroglobulin concentrations would be expected to be low, and of course the recurrence rate should be low. And it was.

However one may speculate about the pathophysiology of antithyroglobulin antibody production in patients with thyroid carcinoma, the practical reality is that the presence of the antibodies complicates follow-up of the patients. They interfere with measurements of serum thyroglobulin, although the extent of the interference and whether it can be corrected for by recovery studies is debated. If they predict recurrence, then patients with high serum antibody concentrations may need closer, and more complicated, follow-up.

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Some women with hyperemesis gravidarum have transient hyperthyroidism

Tan JY, Loh KC, Yeo GS, Chee YC. Transient hyperthyroidism of hyperemesis gravidarum. BJOG 2002;109:683-8.

SUMMARY

Background Pregnant women have transient increases in thyroid secretion, manifested by a small increase in serum free thyroxine (T_4) concentrations and a small decrease in serum thyrotropin (TSH) concentrations, from approximately 6 to 16 weeks of gestation, caused by the thyroid-stimulating action of chorionic gonadotropin. These changes are exaggerated in women with hyperemesis gravidarum, sometimes so much so that they may be thought to have hyperthyroidism caused by Graves' disease (and to need antithyroid-drug therapy). This case study was done to define the clinical and biochemical characteristics and course of women with hyperemesis gravidarum who had hyperthyroidism, and to compare the findings in these women with the findings in pregnant women with Graves' hyperthyroidism.

Methods The study subjects were women with hyperemesis gravidarum, defined as persistent vomiting beginning before 13 weeks of gestation that was so severe that the woman could not retain solids or liquids and needed to be hospitalized for intravenous hydration for more than three days or on more than one occasion. The women were evaluated by clinical examination; pelvic ultrasonography (to exclude trophoblastic disease); and measurements of serum TSH, free T_4, TSH receptor antibodies, thyroid peroxidase antibodies, electrolytes, alanine and aspartate aminotransferases, and bilirubin. Many of these tests were done weekly until normal. Hyperthyroidism was defined as a serum TSH concentration <0.1 mU/L and a serum free T_4 concentration >2.0 ng/dL (26 pmol/L).

Results Among 78 women hospitalized for treatment of hyperemesis gravidarum, 39 had transient hyperthyroidism. Their mean age was 30 years (range, 19 to 40); the mean duration of gestation was 9 weeks (range, 6 to 13); 35 had singleton pregnancies and 4 twin pregnancies; and 19 had one admission, 8 had two admissions, and 12 had three or more admissions. Twenty-two women (56 percent) had lost >5 percent of their prepregnancy weight. None had clinical manifestations of hyperthyroidism or Graves' disease. At first admission, 26 of the 39 women (67 percent) had hyponatremia, 23 (59 percent) had hypokalemia, 22 (56 percent) had high serum aminotransferase concentrations, and 5 (13 percent) had hyperbilirubinemia. None had a high serum concentration of TSH receptor antibodies, and 2 (5 percent) a high serum antithyroid peroxidase antibody concentration.

The peak mean serum free T_4 concentration in these 39 women was 3.1 ng/dL (40 pmol/L) at 9 weeks of gestation, after which the values fell progressively; all the women had normal serum free T_4 concentrations by 15 weeks. Serum TSH concentrations increased more slowly, but all the women had serum TSH concentrations ≥0.1 mU/L by 19 weeks. One woman had a spontaneous abortion at 15 weeks; the remainder delivered at term. The infants of women who had lost >5 percent of their prepregnancy weight were slightly smaller than the infants of the women who lost less or no weight (2915 vs. 3115 g, P = 0.09). The ratio of female to male infants was 2.6:1.

Five women were thought to have Graves' hyperthyroidism, based on the presence of persistent tachycardia, goiter, or ophthalmopathy, and high serum concentrations of TSH receptor antibodies or antithyroid peroxidase antibodies. Three of these women were not treated, and improved spontaneously, and two were treated with propylthiouracil.

Conclusion Some women with hyperemesis gravidarum have transient hyperthyroidism, which subsides during the second trimester, and thereafter their pregnancies and deliveries are normal.

COMMENTARY

The hyperthyroidism that occurs in some women with hyperemesis gravidarum is true hyperthyroidism. Compared with normal pregnant women, their serum free T_4 concentrations are higher and their serum TSH concentrations are lower. Their thyroid secretion must be increased more and the increase lasts longer. The increase in thyroid secretion in both groups is caused by chorionic gonadotropin, and there is a positive correlation between serum chorionic gonadotropin concentrations and serum free T_4 concentrations in both normal pregnant women and women with hyperemesis gravidarum (1).

The hyperthyroidism in these women is not, however, clinically important. The women do not have any clinical manifestations of hyperthyroidism or thyroid enlargement, presumably because the increase in thyroid secretion is small and transient, and the illness is dominated by the hyperemesis and the attendant abnormalities in serum electrolyte concentrations. The hyperemesis is probably due to excess estrogen production caused by the excess production of chorionic gonadotropin. Conversely, pregnant women with hyperthyroidism caused by Graves' disease do have clinical manifestations of hyperthyroidism and often thyroid enlargement, they have more severe biochemical hyperthyroidism, and they do not have hyperemesis. It is on the basis of these differences that these two causes of gestational hyperthyroidism can be distinquished.

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Discordance of thyroid dysgenesis in monozygotic twins

Perry R, Heinrichs C, Bourdoux P, Khoury K, Szots F, Dussault JH, Vassart G, Van Vliet G. Discordance of monozygotic twins for thyroid dysgenesis: implications for screening and for molecular pathophysiology. J Clin Endocrinol Metab 2002;87:4072-7.

SUMMARY

Background Thyroid dysgenesis, in the form of thyroid agenesis, hypoplasia, or ectopy, accounts for approximately 85 percent of cases of congenital hypothyroidism in iodine-sufficient regions of the world. The remainder have defects in thyroid hormone biosynthesis (dyshormonogenesis), which are inherited as autosomal recessive traits. The causes of thyroid dysgenesis are not known. A few infants have had homozygous mutations in the gene for one of the thyroid transcription factors or the thyrotropin (TSH) receptor, and approximately 2 percent of cases are familial. In this study the concordance of congenital hypothyroidism among twins was evaluated, and in addition the possibility that mixing of blood among twins might alter the results of screening for congenital hypothyroidism was studied.

Methods The initial study subjects were monozygotic twins born in Quebec in 2000 who were discordant for congenital hypothyroidism. The affected twin had only a slightly high screening blood TSH concentration (22 mU/L). Eleven days later this infant had a very high serum TSH concentration (444 mU/L) and a low serum free thyroxine (T_4) concentration (0.3 ng/dL [3.4 pmol/L]). The multiyear records of the Quebec, Canada and Brussels, Belgium screening programs were searched to identify twins with congenital hypothyroidism, and the infants' records were then reviewed. In addition, pediatric endocrinologists in Quebec and Brussels were surveyed to determine if they knew of any twins with congenital hypothyroidism missed by the screening programs.

Results During the study interval, the frequency of congenital hypothyroidism was 1 in 2971 infants in Quebec and 1 in 3167 infants in Brussels. Sixteen pairs of twins were identified in the two regions, of which five were monozygotic twins and 11 were dizygotic twins. All the twin pairs were discordant for congenital hypothyroidism. The causes of the hypothyroidism were thyroid dysgenesis in one infant in each of five monozygotic pairs and one infant in each of seven dizygotic pairs, and dyshormonogenesis in one infant in each of four dizygotic pairs. Thyroid ultrasonography, done in the normal twin of four twin pairs, was normal. The mothers of all the infants had normal thyroid function, and there was only one case of congenital hypothyroidism in each family. The survey of pediatric endocrinologists did not reveal any twins missed by the neonatal screening programs.

Exact values for screening blood TSH concentrations and follow-up serum values at the time of recall were available for four infants with congenital hypothyroidism from pairs of monozygotic twins. The results in these four infants and 16 singleton infants with congenital hypothyroidism matched for age at screening and diagnosis and serum TSH values at diagnosis suggest that mixing of blood between affected and unaffected twins lowers screening blood TSH values in affected twins (65 versus 160 mU/L) (Table).

Table. Times of Testing and Blood and Serum TSH Values (Range) of Monozygotic Twins with Congenital Hypothyroidism and Matched Singleton Infants with Congenital Hypothyroidism.

	Monozygotic Twins (n=4)	Singleton Infants (n=16)
Mean age at screening (days)	3 (2-5)	3 (2-5)
Blood TSH value at screening (mU/L)	65 (22-204)	160 (29-499)
Age at diagnosis (days)	19 (14-22)	14 (9-23)
Serum TSH at diagnosis (mU/L)	519 (406-985)	532 (368-999)

Conclusion Monozygotic twins are rarely concordant for congenital hypothyroidism caused by thyroid dysgenesis. Fetal blood mixing may mask congenital hypothyroidism in affected twins.

COMMENTARY

The success of newborn screening programs for congenital hypothyroidism has not been matched by comparable success in understanding of the causes of congenital hypothyroidism. This is particularly true for its most common cause, thyroid dysgenesis. This is an all-purpose term that encompasses multiple abnormalities in thyroid development, from complete absence of thyroid tissue (agenesis), to a decreased amount of thyroid tissue in an abnormal location (ectopia), to an inadequate amount of thyroid tissue in the normal location (hypoplasia). This study does not provide evidence for a major genetic component in the causation of thyroid dysgenesis, but not many twin pairs were identified. Other evidence, however, does support the possibility of a genetic contribution. In a study of 241 first-degree relatives of 84 infants with congenital hypothyroidism, 21 thyroid developmental abnormalities were detected by ultrasonography in 19 relatives (8 percent). as compared with 2 of 217 subjects (1 percent) from families with no thyroid disorder (1). Detailed analysis of these results suggested that in some families thyroid dysgenesis is transmitted as an autosomal dominant trait. In the majority, however, it is an isolated event, probably caused by an early somatic mutation or an environmental insult..

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Thyroid abnormalities in recipients of bone marrow transplants are usually associated with chronic graft-versus-host disease

Tauchmanova L, Selleri C, De Rosa G, Pagano L, Orio F, Lombardi G, Rotoli B, Colao A. High prevalence of endocrine dysfunction in long-term survivors after allogeneic bone marrow transplantation for hematologic diseases. Cancer 2002;95:1076-84.

SUMMARY

Background Bone marrow transplantation is an effective therapy for several hematologic diseases, but has numerous complications. They include endocrine dysfunction, caused by the pretransplant conditioning regimen, graft-versus-host disease (GVHD), or immunosuppressive therapy. In this study endocrine function was evaluated in a group of patients who had received allogeneic bone marrow transplants.

Methods The study subjects were 40 patients (21 women, 19 men; age at the time of transplantation, 29 years [range, 13 to 45]) with hematologic disease who received bone marrow-derived stem cells from HLA-identical siblings and who were disease-free one or more years after transplantation. Twenty-two patients had acute leukemia, 16 had chronic leukemia, and 2 had aplastic anemia. The pretransplant conditioning regimen consisted of busulfan and cyclophosphamide (no patient received radiation). Cyclosporine and methotrexate were given as prophylaxis against acute GVHD. Acute GVHD was treated with high doses of glucocorticoids, and chronic GVHD with high doses of glucocorticoids and cyclosporine. Thirteen patients (32 percent) had acute GVHD, and 26 patients (65 percent) had chronic GVHD. The median duration of follow-up was 38 months (range, 12 to 62).

Results Pituitary-Thyroid Function Twenty patients were known to have normal thyroid function before transplantation. After transplantation, 20 patients were studied once and 20 on several occasions. Twelve patients (30 percent) had some abnormality in thyroid function. Four patients with chronic GVHD 12 to 48 months after transplantation had low serum free triiodothyronine concentrations and normal serum free thyroxine and thyrotropin (TSH) concentrations, findings considered to be caused by their nonthyroidal illness. Six patients had subclinical hyperthyroidism when first studied 12 to 18 months after transplantation; the three patients studied again 4 to 7 months later had normal serum TSH concentrations. Two patients had subclinical hypothyroidism 5 and 6 years after transplantation. Four of the patients with subclinical hyperthyroidism and both patients with subclinical hypothyroidism had chronic GVHD. One patient had a thyroid lymphoma 8 months after transplantation.

Pituitary-Gonadal Function Among the 21 women, 20 (95 percent) had amenorrhea, and 1 (5 percent) polymenorrhea. All had high serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations, low serum estradiol concentrations, and normal serum prolactin concentrations. Two women recovered; the others were considered to have permanent primary hypogonadism. The 19 men had normal serum LH and testosterone concentrations, but 9 (47 percent) men had high serum FSH concentrations; all 3 men who were tested had azoospermia.

Pituitary-Adrenal Function All 40 patients received glucocorticoid therapy; the median dose was 10 g/m^2 of prednisone or its equivalent (range, 0.9 to 24), and the median duration of therapy was 9 months (range, 3 to 36). Four patients (10 percent) had secondary adrenal insufficiency when studied 10 to 30 days after the cessation of glucocorticoid therapy; all had normal adrenal function 6 to 18 months later. The other 36 patients (90 percent) had normal adrenal function when studied 30 to 180 days after the cessation of glucocorticoid therapy.

Growth Hormone-Insulin-Like Growth Factor I All patients had normal serum growth hormone concentrations, measured in six samples collected at 20-minute intervals for two hours. Serum insulin-like growth factor I concentrations were lower than in age-matched normal subjects in 10 of the 26 patients (38 percent) with chronic GHVD, but only 1 of the 14 other patients (7 percent).

Conclusion Among patients with hematologic diseases treated with allogeneic bone marrow transplantation, endocrine dysfunction is common, especially in patients with chronic GVHD.

COMMENTARY

Endocrine dysfunction was most commonly found in the patients with GVHD, but were the abnormalities caused by the GVHD or by the high doses of glucocorticoids or other immunosuppressive drugs given to treat GVHD?

Acute or chronic GVHD alone would be expected to cause the same changes in thyroid function as any other illness, namely low serum free triiodothyronine concentrations alone, low serum TSH concentrations alone (transient subclinical hyperthyroidism), or both. High doses of glucocorticoids have similar effects. GVHD alone might also cause thyroid dysfunction, if the donor cells recognized recipient thyroid cells as nonself, causing thyroid inflammation.

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3,5-Diiodothyropropionic acid has favorable short-term effects on cardiac hemodynamics in patients with congestive heart failure

Morkin E, Pennock G, Spooner PH, Bahl JJ, Underhill Fox K, Goldman S. Pilot studies on the use of 3,5-diiodothyropropionic acid, a thyroid hormone analog, in the treatment of congestive heart failure. Cardiology 2002;97:218-225.

SUMMARY

Background Patients with congestive heart failure often have low serum triiodothyronine (T_3) concentrations, which may contribute to their decreased cardiac contractility and increased peripheral resistance. Thyroid hormones increase cardiac contractility and decrease peripheral resistance, but have many other actions; these actions may to some extent be dissociated in some thyroid hormone analogs. This study evaluated the effects of 3,5-diiodothyropropionic acid (DITPA), a thyroid hormone analog that in animals has relatively greater inotropic than chronotropic and metabolic effects, in normal subjects and patients with congestive heart failure.

Methods The study subjects were seven normal men (age range, 18 to 65 years) and 21 patients with congestive heart failure (numbers of women and men not given; age range, 47 to 67 years). All the patients had symptoms of heart failure, sinus rhythm, a cardiac ejection fraction <35 percent, and a New York Heart Association functional class of II or III; 20 patients had ischemic cardiomyopathy and 1 patient had dilated cardiomyopathy. They could be taking digoxin, an angiotensin-converting enzyme inhibitor, and a diuretic, but not a β-adrenergic antagonist.

The normal subjects were given 1.875 mg/kg of DITPA in two divided doses daily for two weeks and then 3.75 mg/kg daily for two weeks. The patients with heart failure were randomly assigned to receive 1.875 mg/kg of DITPA in divided doses daily for two weeks and then 3.75 mg/kg daily for two weeks, or placebo. Body weight, heart rate, blood pressure, and serum thyroxine (T_4) and thyrotropin (TSH) were measured before and at the end of each treatment period. Serum T_3 was not measured at base line in the patients with heart failure, and it was not measured during DITPA treatment because it cross-reacted in the T_3 assay. The patients underwent cardiac catheterization, echocardiography, and measurements of ejection fraction by radionuclide imaging at base line and four weeks.

Results Normal Subjects There were no changes in weight, heart rate, or blood pressure after administration of DITPA for two and four weeks. The mean serum TSH concentration fell from 3.5 mU/L to 0.4 mU/L at four weeks; the mean serum T_4 concentrations at these times were 8.7 μg/dL (112 nmol/L) and 5.9 μg/dL (76 nmol/L), respectively, but the mean serum free T_4 concentration did not change.

Patients with Congestive Heart Failure Nineteen patients completed the study, 9 in the DITPA-treatment group and 10 in the placebo group. At base line, the DITPA and placebo groups were similar, except that the mean ejection fraction was lower in the DITPA group (18 vs. 29 percent). During treatment, there were no changes in weight, heart rate, or blood pressure in either group. The mean serum TSH concentration decreased from 2.5 mU/L to 0.02 mU/L in the DITPA-treatment group, but the mean serum free T_4 concentration did not change; there were no changes in either hormone in the placebo group. The mean serum low-density-lipoprotein cholesterol and triglyceride concentrations decreased in the DITPA-treatment group, but did not change in the placebo group.

There were no changes in functional class, ejection fraction, and echocardiographic measurements (fractional shortening, velocity of circumferential fiber shortening, and ratio of early to late diastolic filling) in either group, except for a decrease in the velocity of circumferential fiber shortening in the DITPA-treatment group. Similarly, there were no changes in pulmonary artery, right atrial, or mean arterial pressure in either group. The mean cardiac index increased by 17 percent ($P = 0.04$) and the mean systemic vascular resistance index decreased by approximately 15 percent (extrapolated from Figure 2, $P = 0.02$) in the DITPA-treatment group; these measurements did not change in the placebo group.

Conclusion The thyroid hormone analog DITPA increases cardiac output and decreases peripheral vascular resistance in patients with congestive heart failure.

COMMENTARY

DITPA increased cardiac output, presumably by improving diastolic function and decreasing peripheral vascular resistance, in patients with congestive heart failure. Its prolonged administration would be expected to result in improvement in symptoms and functional class, if the increase were sustained and no harmful chronotropic effects occurred. The authors suggest that it did not increase myocardial oxygen consumption, because the product of the heart rate times the mean arterial pressure did not increase. However, DITPA can hardly be said to have specific cardiac effects; it inhibited TSH secretion and lowered serum lipid concentrations. The search for cardiac-specific and other organ-specific thyroid hormone analogs will continue, now spurred by recognition that there are several nuclear receptors for thyroid hormone with different tissue distributions.

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Recurrence of mild iodine deficiency in Tasmania

Guttikonda K, Burgess JR, Hynes K, Boyages S, Byth K, Parameswaran V. Recurrent iodine deficiency in Tasmania, Australia: a salutary lesson in sustainable iodine prophylaxis and its monitoring. J Clin Endocrinol Metab 2002;87: 2809-15.

SUMMARY

Background Endemic goiter was common in Tasmania before 1950. Iodine supplementation began that year with the distribution of potassium iodide tablets to schoolchildren. In 1966 this was replaced by the addition of potassium iodate to bread. During the 1960s the presence of iodine in milk, due to the use of iodine-containing disinfectants in dairy cattle, led to a further increase in iodine intake. A maximum (but no minimum) limit was then mandated for iodine content in milk, and addition of potassium iodate to bread was discontinued. From the late 1960s to the mid-1980s, iodine intake was considered adequate, based on measurements of urinary iodine. Monitoring of the iodine content of milk lapsed in the late 1980s. By the 1990s, as dairy-farming practices changed, some children had urinary iodine values <50 μg/L, indicative of moderate dietary iodine deficiency. This study was undertaken to evaluate contemporary iodine nutrition in Tasmania 50 years after iodine supplementation was introduced.

Methods The study subjects were 225 children (99 girls, 126 boys; mean age, 11 years [range, 4 to 17]). Morning urine samples were collected for the measurement of iodine, and thyroid volume was measured by ultrasonography. Thyroid volume, corrected for age and body surface area, was classified as normal or increased according to uncorrected and corrected standards of the World Health Organization/International Council for the Control of Iodine Deficiency Disorders (WHO/ICCIDD).

Results The median urinary iodine excretion in the 225 children was 84 μg/L (interquartile range, 57 to 110); 20 percent of the children had values of 50 μg/L or lower, indicative of moderate iodine deficiency. The median values were similar in girls and boys (81 vs. 84 μg/L). There was some regional variation within the state, but not among children of differing socioeconomic status.

The prevalence of thyroid enlargement in the girls was 3.5 percent based on age and on body-surface area in relation to the uncorrected WHO/ICCIDD standards, and it was 21 percent based on age and body-surface area in relation to the corrected standards. For the boys, the prevalence of thyroid enlargement was 5 percent based on age and 6 percent based on body-surface area in relation to the uncorrected standards, and 25 percent based on age and 22 percent based on body-surface area in relation to the corrected standards. There were no differences in thyroid volume in the girls and boys, or among children living in different areas of the state or having different socioeconomic status.

Conclusion Among school children in Tasmania, the values for urinary iodine excretion and the percentages with thyroid enlargement indicate the recurrence of mild iodine deficiency.

COMMENTARY

The standard measures of iodine nutrition are the presence or absence of goiter, preferably determined by ultrasonography, and urinary iodine excretion. In many studies around the world the measurements of thyroid volume were compared with those of iodine-sufficient Europeans, but there has been increasing recognition that the values are lower in iodine-sufficient people living elsewhere, due at least in part to differences in body size. A correction factor has been introduced to adjust for these differences. Correction of values nearly always leads to an increase in the frequency of goiter, as in this study. Urinary iodine excretion closely reflects iodine intake, but can vary from day to day.

The history of the ups and downs of iodine supplementation in Tasmania provides important lessons on the factors that can affect iodine intake in different populations, and these lessons are undoubtedly applicable to other countries. In Tasmania, the introduction of iodine-containing disinfectants in the dairy industry and the subsequent reduction in the use of these products had major impacts on iodine nutrition.

The same thing has happened in the United States. In 1971-1974, the median urinary iodine excretion was 320 μg/L, whereas in 1988-1994 it was 145 μg/L (1). And at the latter time urinary iodine excretion was <50 μg/L in 12 percent of the population, including 15 percent of pregnant women. The causes of this marked decrease in urinary iodine excretion include decreased use of salt, including iodized salt, in home cooking; decreased use of iodized salt in manufactured foods and restaurants; cessation of use of potassium iodate in the baking industry; and decreased use of iodine-containing animal feeds and iodine-containing disinfectants in animals.

The important point is that changes in iodine intake can be caused by changes in farming or food industry practices that have little to do with iodine nutrition in humans, as well by variations in the content of iodine occurring naturally in food and water. Iodine deficiency should never be considered to be permanently eliminated, and iodine intake should be continually monitored in all countries.

Robert D. Utiger, M.D.

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