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Robert D. Utiger, M.D.

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Subclinical hypothyroidism but not subclinical hyperthyroidism is associated with an increase in fatal and nonfatal coronary heart disease

Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med* 2005;165:2467-72.

SUMMARY

Background Thyroid dysfunction, particularly subclinical thyroid dysfunction (low or high serum thyrotropin [TSH] and normal free thyroxine [T₄] concentrations), is common, as are cardiovascular diseases, but whether either subclinical hypothyroidism or subclinical hyperthyroidism is a risk factor for cardiovascular diseases is not clear. In this study, the frequency of cardiovascular diseases, in particular coronary heart disease, was determined both cross-sectionally and longitudinally in euthyroid subjects and subjects with subclinical hypothyroidism or subclinical hyperthyroidism.

Methods The study subjects were 2064 subjects (1015 women, 1049 men; mean age, 50 years [range, 17 to 89]) living in Busselton, a rural town in Western Australia. The subjects, most of whom were white, were enrolled in the study in 1981, at which time they completed health and life-style questionnaires and had an electrocardiogram and measurements of serum TSH (normal, 0.4 to 4.0 mU/L), free T₄, and cholesterol. The presence of coronary heart disease was diagnosed on the basis of history and electrocardiography.

The mortality from cardiovascular disease and the morbidity and mortality from coronary heart disease among these subjects through 2001 was determined by review of the death and hospital registries for Western Australia.

Results At base line, 119 subjects (6 percent) had subclinical hypothyroidism, 1906 (92 percent) had normal serum TSH concentrations, and 39 (2 percent) had subclinical hyperthyroidism (Table). As compared with the euthyroid subjects, coronary heart disease was more common in those with subclinical hypothyroidism (odds ratio, 2.2; P = 0.01), but not in those with subclinical hyperthyroidism (odds ratio, 0.5; P = 0.36). Among the subjects with subclinical hypothyroidism, the association with coronary heart disease was significant only in those with serum TSH concentrations >10 mU/L.

Table. Coronary Heart Disease at Base Line in the Three Study Groups.

	Subclinical Hypothyroidism (n=119)	Euthyroid (n=1906)	Subclinical Hyperthyroidism (n=39)
Women/men	82/37	912/994	21/18
Median serum TSH (mU/L)	6.3	1.4	0.3
Mean serum free T ₄ (ng/dl)*	1.1	1.2	1.4
Coronary heart disease	18 (15%)	154 (8%)	2 (5%)
Prevalence odds ratio (95% CI)**	2.2 (1.2-4.0)	1.0	0.5 (0.1-2.4)

*To convert to serum free T₄ values to pmol/L, multiply by 12.9.
**CI denotes confidence interval. Adjusted for age, sex, smoking status, exercise, body-mass index, blood pressure, diabetes mellitus, and serum cholesterol.

Among the 1890 subjects who did not have coronary heart disease at base line, the death rate from cardiovascular disease during follow-up was no higher in the 101 subjects with subclinical hypothyroidism than in the 1752 euthyroid subjects (hazard ratio, 1.5; P = 0.10, adjusted for age, sex, and additional factors [see footnote in Table 1]). There also was no increase in cardiovascular mortality in the subjects with subclinical hyperthyroidism.

The risk of fatal and nonfatal coronary heart events among these subjects was higher in those with subclinical hypothyroidism, after adjustment for age and sex (hazard ratio, 1.7; P<0.01) and after additional adjustments (hazard ratio, 1.8; P<0.01). Among the subjects with subclinical hypothyroidism, the increase in coronary events was higher in the subjects with serum TSH values >10 mU/L (hazard ratio, 2.6; P<0.01) than in those with values >4.0 to 10 mU/L (hazard ratio, 1.6, P = 0.04).

The rates of fatal and nonfatal coronary events were similar in the subjects with serum TSH values of 0.4 to 2.0 mU/L, those with values of >2.0 to 4.0 mU/L, and those with subclinical hyperthyroidism.

Conclusion Prevalent and incident coronary heart disease is more common in subjects with subclinical hypothyroidism, as compared with those with normal serum TSH values, but is not more common in subjects with subclinical hyperthyroidism.

COMMENTARY

These studies address a controversial question—does subclinical hypothyroidism cause cardiovascular disease? Most longitudinal studies have suggested not, but the suspicion remains. Furthermore, there is evidence that it has some deleterious effects on cardiovascular function (1), but whether these effects are clinically important is not clear.

The results of these two studies suggest that subjects with more than a small increase in serum TSH concentrations do have a small increase in risk for diverse cardiovascular disorders, but not mortality. Why the risk of incident coronary heart disease was increased in these subjects in one study but not the other is not obvious; possible explanations include differences in race/ethnicity, life style, age at base line, methods of ascer-

tainment of coronary disease, differences in adjustments for known risk factors for cardiovascular disease, and duration of follow-up. Congestive heart failure has not been evaluated before.

The finding in both studies that subjects with higher serum TSH values were more likely to have some cardiovascular abnormality lends credence to the notion that subclinical hypothyroidism does have deleterious cardiovascular

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Subclinical hypothyroidism is associated with an increase in congestive heart failure but not other cardiovascular diseases

Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med* 2005;165:2460-6.

SUMMARY

Background Subclinical hypothyroidism may have deleterious effects on cardiac function, and it has been associated with cardiovascular disease. This study was done to determine the risk of heart failure and other cardiovascular disorders in subjects with subclinical hypothyroidism.

Methods The study subjects were 2730 Medicare-eligible community-dwelling people aged 70 to 79 years (51 percent women, 40 percent black) living in Memphis and Pittsburgh who were enrolled in the Health, Aging, and Body Composition Study in 1997. At base line, the subjects completed questionnaires about life style, education, and health, and their weight, height, blood pressure, and serum thyrotropin (TSH) (subjects with values >0.1 and <4.5 mU/L were considered euthyroid), free thyroxine, and total cholesterol were measured. Prevalent cardiovascular disease (coronary heart disease, stroke, peripheral arterial disease, and congestive heart failure) was diagnosed on the basis of self-reported history and review of Medicare records.

Subsequently, the subjects were followed up at 6-month intervals, at which times data about health status, hospitalizations, and procedures were obtained, for four years. Diagnoses were based on review of these data by clinicians unaware of the subject's thyroid status. Cardiovascular events were defined as death or hospitalization for coronary heart disease (angina, myocardial infarction, or a revascularization procedure), stroke (or transient ischemia), peripheral arterial disease, and congestive heart failure.

Results At base line, 338 (12 percent) of the 2730 subjects had subclinical hypothyroidism, of whom 55 percent were women and 25 percent were black. As compared with the 2392 euthyroid subjects, they were more active physically and had a slightly lower body-mass index, more were taking thyroid hormone (15 vs. 8 percent), and their serum total cholesterol concentration was higher, by 7 mg/dl (0.2 mmol/L). The prevalence of cardiovascular disease and congestive heart failure in the two groups was similar.

During the 4-year follow-up period, the incidence of congestive heart failure was higher in the subjects with high base-line serum TSH values than in the euthyroid subjects (Table). The event rates were 16 per 1000 person-years in the euthyroid subjects and 21 per 1000 person-years in the subjects with subclinical hypothyroidism; among the latter the rates were 15, 34, and 37 per 1000 person-years, respectively, in the subjects with serum TSH values ≥ 4.5 to 6.9, 7.0 to 9.9, and ≥ 10 mU/L (hazard ratios, 1.07, 2.58, and 3.02, respectively).

Table. Numbers of Congestive Heart Failure and Other Cardiovascular Events in Euthyroid Subjects and Subjects with Subclinical Hypothyroidism during Follow-up for Four Years.

	Euthyroid (n=2392)	Subclinical Hypothyroidism (n=338)	Hazard Ratio (95% CI)*
Congestive heart failure	151 (6%)	27 (8%)	1.61 (1.02-2.52)
Coronary heart disease	298 (34%)	36 (29%)	0.85 (0.58-1.26)
Stroke	131 (15%)	22 (18%)	1.37 (0.85-2.20)
Peripheral arterial disease	72 (8%)	11 (9%)	1.33 (0.67-2.64)

*CI denotes confidence interval. Adjusted for age, race, socioeconomic status, smoking, and multiple illness-related covariates.

A total of 334 subjects (12 percent) had a coronary heart disease event (myocardial infarction, 98), 153 (6 percent) had a stroke, and 83 (3 percent) had peripheral arterial disease during follow-up. The rates of these events were similar in the euthyroid subjects and the subjects with subclinical hypothyroidism as a whole (Table) and also in the three subgroups with high serum TSH values as defined in the preceding paragraph.

There were 104 deaths (4 percent) from cardiovascular disease and 324 deaths (12 percent) from all causes. The rates of these events also were similar in the euthyroid subjects and the subjects with subclinical hypothyroidism.

Conclusion Among older subjects, subclinical hypothyroidism is associated with an increased frequency of congestive heart failure, but not of coronary heart disease, stroke, or peripheral arterial disease or mortality from cardiovascular disease.

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effects, even if the effects were different in the two studies.

One would like to know more about what happened to these subjects during follow-up. By definition, they had normal serum free T₄ concentrations, but how much did the concentrations vary among the groups and subgroups? Did the subjects with subclinical hypothyroidism at

base line have persistent or increasingly severe hypothyroidism, or did it remit? Were any of the subjects treated with T₄? The answers might provide some insights into the reported associations, as well as more information about the natural history of subclinical hypothyroidism.

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Robert D. Utiger, M.D.

Sexual dysfunction is common in men with hyperthyroidism or hypothyroidism

Carani C, Isidori AM, Granata A, Carosa E, Maggi M, Lenzi A, Jannini EA. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *J Clin Endocrinol Metab* 2005;90:6472-9.

SUMMARY

Background Hyperthyroidism and hypothyroidism are less common in men than in women, and there have been few studies of the effects of these disorders on sexual function in men. In this study, sexual and pituitary–gonadal function were assessed in men with hyperthyroidism or hypothyroidism before and after treatment.

Methods The study subjects were 34 men with hyperthyroidism and 14 men with hypothyroidism. Their mean (\pm SD) age was 43 years, with no difference between the two groups. All were in a stable relationship (>1 year). The cause of the hyperthyroidism was Graves' disease in 19 men (56 percent), multinodular goiter in 9 (26 percent), and a thyroid adenoma in 6 (18 percent). All the men with hypothyroidism had chronic lymphocytic thyroiditis. The men were consecutively encountered, but men with a history of sexual dysfunction and those with cardiac disease, diabetes mellitus, and prostatic disease were excluded. The men with hyperthyroidism were treated with methimazole, and those with hypothyroidism with thyroxine.

At base line and at least 8 weeks after restoration of euthyroidism (median, 10 weeks; range, 8 to 16), the men were asked about sexual desire, erectile function, premature ejaculation, and delayed ejaculation using a standardized questionnaire, and pituitary–thyroid and pituitary–gonadal hormones were measured.

Results Six of the 48 men (12 percent) spontaneously reported abnormal sexual function after the onset of thyroid dysfunction (group distribution not described), whereas 45 (94 percent) reported abnormal sexual function when asked. The results of the pituitary–thyroid function tests were diagnostic of hyperthyroidism or hypothyroidism at base line and normal at the time of the follow-up study.

Among the 34 men with hyperthyroidism, 1 to 17 (3 to 50 percent) had one or more of the four abnormalities in sexual function (Table). Their mean serum testosterone, estradiol, and sex hormone-binding globulin (SHBG) concentrations were near the upper limit of the normal range, and their mean serum free testosterone, luteinizing hormone (LH), and prolactin concentrations were normal. With treatment, sexual function improved considerably (the largest change was a decrease in frequency of premature ejaculation), and mean serum testosterone, estradiol, and SHBG concentrations decreased by approximately 30 percent.

Table. Frequency of Sexual Dysfunction before and after Treatment in Men with Hyperthyroidism or Hypothyroidism.

	Hyperthyroidism (n=34)		Hypothyroidism (n=14)	
	Base Line	Treatment	Base Line	Treatment
Decreased sexual desire	6 (18%)	2 (6%)	9 (64%)	5 (36%)
Erectile dysfunction	5 (15%)	1 (3%)	9 (64%)	3 (21%)
Premature ejaculation	17 (50%)	5 (15%)	1 (7%)	1 (7%)
Delayed ejaculation	1 (3%)	1 (3%)	9 (64%)	4 (28%)

Among the 14 men with hypothyroidism, 9 (64 percent) had decreased sexual desire, erectile dysfunction, or delayed ejaculation, and 1 (7 percent) had premature ejaculation (Table). Their mean serum testosterone concentration was low normal, and their serum free testosterone, estradiol, SHBG, LH, and prolactin concentrations were normal. With treatment, the frequency of abnormalities in sexual function decreased substantially, the mean serum testosterone concentration increased by 47 percent, and there was no change in serum SHBG concentrations.

Conclusion In men with hyperthyroidism or hypothyroidism, decreased sexual desire, erectile dysfunction, and premature or delayed ejaculation are common, and the abnormalities decrease in response to appropriate therapy.

COMMENTARY

Decreased sexual desire and ejaculatory dysfunction have previously been described in men with hyperthyroidism, (1) but this study delved further into the men's sexual function, thus providing a clearer picture of the changes that can occur. The changes were not closely correlated with serum thyroid hormone or sex hormone concentrations, and the possibility that they might be related to the neuropsychologic changes of hyperthyroidism was not examined. The hormonal changes were for the most part within the normal range, although the

men's serum SHBG and therefore testosterone, but not free testosterone, concentrations were higher than in normal men, again documenting the effect of hyperthyroidism to increase production of SHBG. Other changes in what might be called the reproductive aspects of hyperthyroidism in men include gynecomastia, attributed to increased peripheral conversion of testosterone to estradiol, and a decrease in spermatogenesis, cause not known (1).

The men with hypothyroidism had less sexual dysfunction, and here, too, the role of the neuropsychologic changes can be questioned. These men have low nor-

mal serum testosterone and SHBG concentrations, indicating that SHBG production is sensitive to thyroxine deficiency as well as to thyroxine excess. Both normal and decreased testicular function have been described in the few studies of men with hypothyroidism (1).

Robert D. Utiger, M.D.

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Hyperthyroidism caused by Graves' disease often occurs soon after childbirth

Benhaim Rochester D, Davies TF. Increased risk of Graves' disease after pregnancy. *Thyroid* 2005;15:1287-90.

SUMMARY

Background Graves' disease and hyperthyroidism, its most common manifestation, are more common in women than men, and their occurrence is determined by both genetic susceptibility and nongenetic factors, including, perhaps, recent pregnancy. This study was done to determine the relative frequency of onset of Graves' hyperthyroidism among nulliparous women, those who had had a recent pregnancy, and those in whom pregnancy was more distant.

Methods The records of 152 consecutive women aged 18 to 39 years with Graves' hyperthyroidism seen at a single clinic in New York City were reviewed. The diagnosis was based on clinical findings, the presence of overt biochemical hyperthyroidism, and a high serum concentration of thyrotropin receptor antibodies (TSHR-Ab, measured by radioreceptor assay) or normal or high thyroid radioiodine uptake at 24 hours. Most of the women were treated with an antithyroid drug, usually for 6 to 12 months, but a few were treated with radioiodine or surgery. The mean duration of follow-up after treatment was 36 months (range, 1 to 222). Relapse was defined as persistent or recurrent hyperthyroidism after any treatment.

Results The 152 women with Graves' hyperthyroidism included 94 nulliparous women (62 percent) and 58 who had been pregnant (38 percent). Among the 58 women who had been pregnant, the onset of hyperthyroidism was ≤ 1 year after delivery in 26 (45 percent [17 percent of the entire group]) and >1 year after delivery in 32 (55 percent [21 percent of the entire group]).

Table. Characteristics and Outcome of Treatment of the Nulliparous, Recently-Pregnant, and Distantly-Pregnant Women with Graves' Hyperthyroidism.

	Pregnancy Status		
	None (n=94)	Recent (n=26)	Distant (n=32)
Mean age (yr)	30	33	32
Mean no. of deliveries	0	2.0	1.9
Ophthalmopathy	30%	23%	39%
High serum TSHR-Ab*	85%	89%	85%
Relapse*	46%	43%	65%

*Serum TSH-R antibodies were measured in 62 to 69 percent and relapse status was known for 81 to 83 percent of the women in the three groups.

There were no statistically significant differences in the frequency of ophthalmopathy or high serum TSHR-Ab values or in the relapse rates in the three groups of women (Table).

Among the women with Graves' hyperthyroidism, the proportion that had been recently pregnant was compared with the proportion of women of the same age who gave birth in New York City in 2001. Among women aged 20 to 39 years old, the respective proportions were 17 and 9 percent (relative risk, 2.1; 95 percent confidence interval, 1.4 to 3.2). Among 5-year subgroups, the difference was greatest in women aged 35 to 39 years; the respective proportions were 24 and 5 percent (relative risk, 5.6; 95 percent confidence interval, 2.8 to 11.0).

Conclusion Among women of childbearing age who have Graves' hyperthyroidism, over one third have been pregnant, and in almost half of them the diagnosis is made ≤ 1 year after delivery.

COMMENTARY

Graves' disease and thyroiditis must be distinguished from one another in any study of hyperthyroidism in postpartum women, or in anyone else for that matter. That was done as well as one could ask in this study, and therefore it seems likely that all the women did have Graves' hyperthyroidism. Had the postpartum women been subdivided according to the time of onset of symptoms, rather than time of diagnosis, there might have been more women in the recently-pregnant group, strengthening the association between recent pregnancy and the onset of the disorder.

On the other hand, given that the women were referred to a specialty clinic at a large hospital, where many who had been pregnant may have delivered and

been followed postpartum, the proportion of postpartum women, particularly recently-pregnant women, may have been higher than is present in the universe of women with Graves' hyperthyroidism, weakening the association. Considering this universe, it is important to remember that the peak age-specific incidence is approximately 40 years (higher in some studies), and therefore that the findings do not apply to a substantial proportion of women with the disorder.

Nonetheless, many women with Graves' hyperthyroidism are in their childbearing years. The finding of a relationship between a recent pregnancy and the onset of the disorder in this study, whether or not its magnitude was underestimated or overestimated, and in other studies (1,2), may help in unraveling some of the factors, such as loss of immune

tolerance or exposure to a new antigen, that lead to the initiation of Graves' disease in genetically susceptible women.

Robert D. Utiger, M.D.

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Transient hyperthyroidism can occur after parathyroidectomy

Stang MT, Yim JH, Challinor SM, Bahl S, Carty SE. Hyperthyroidism after parathyroid exploration. *Surgery* 2005;138:1058-65.

SUMMARY

Background Surgical treatment of hyperparathyroidism usually involves some manipulation of the thyroid gland, and the occurrence of hyperthyroidism soon after parathyroidectomy has been described. This study evaluated thyroid function in a large group of patients with primary hyperparathyroidism after parathyroidectomy.

Methods The study subjects were 199 consecutive patients (144 women, 55 men; mean age, 58 years) undergoing initial surgery for primary hyperparathyroidism in whom serum thyrotropin (TSH) was measured 7 to 21 days after surgery. Serum TSH was measured preoperatively in 126 patients. Patients who had previous thyroid surgery, were taking thyroid hormone, or underwent bilateral thyroidectomy during parathyroidectomy were excluded.

The exploration and parathyroid resection were unilateral in 131 patients (66 percent) and bilateral in 68 (34 percent). Most patients were discharged on the same day, with instructions to take calcium. They were asked to return 7 to 10 days after surgery, at which time they were asked about symptoms and examined, and serum TSH and calcium were measured. Serum thyroxine (T₄), free T₄ index, and triiodothyronine (T₃) were measured in patients who had a low serum TSH concentration (whether at the same time or a few days later is not stated). Patients with low serum TSH concentrations and normal serum free T₄ index and T₃ values (subclinical hyperthyroidism) were followed, and those with high serum free T₄ index or T₃ values (overt hyperthyroidism) were referred to an endocrinologist.

Results The parathyroid abnormality was a solitary adenoma in 179 patients (90 percent), a double adenoma in 8 (4 percent), hyperplasia in 10 (5 percent), and a carcinoma in 1 (1 percent). The patients were followed for 5 to 36 months;

2 patients had persistent hyperparathyroidism and 1 patient recurrent hyperparathyroidism. Serum TSH concentrations were low 7 to 21 days after surgery in 58 patients (29 percent), normal in 132 (66 percent), and high in 9 (5 percent).

Among the 126 patients in whom serum TSH was measured before surgery, 1 (1 percent) had a low value, which persisted, and 125 (99 percent) had normal values. The mean preoperative serum TSH concentration in these 125 patients was 2.0 mU/L, and it was 1.2 mU/L postoperatively; at that time 39 (31 percent) had low values.

Twenty of these 39 patients (51 percent) had subclinical hyperthyroidism. They had few, if any, symptoms; their mean preoperative and nadir postoperative serum TSH concentrations were 1.5 and 0.1 mU/L, respectively; and their serum TSH concentrations were normal 12 to 243 days (mean, 44) after surgery. The other 19 patients (49 percent) had overt hyperthyroidism. Five of them were considered sufficiently symptomatic to require antithyroid drug therapy (hyperthyroid subgroup), which was given for 48 to 254 days. The other 14 had some symptoms (symptomatic subgroup), but were not treated. The serum TSH concentrations were normal by 34 to 200 days (mean, 92) after surgery in the hyperthyroid subgroup and by 24 to 113 days (mean, 61) in the symptomatic subgroup.

No demographic or clinical variables were associated with low postoperative serum TSH concentrations. Among surgical variables, bilateral neck exploration and no concurrent thyroid lobectomy were associated with low postoperative serum TSH concentrations.

Conclusion Patients with primary hyperparathyroidism may have transient subclinical or overt hyperthyroidism after parathyroid surgery.

COMMENTARY

These patients had traumatic thyroiditis, or more specifically post-parathyroidectomy thyroiditis. This study is the third, and largest, prospective study of thyroid function after parathyroid surgery. In the two earlier studies, 4 of 20 patients (20 percent) and 9 of 26 patients (35 percent) had transient hyperthyroidism during the postoperative period (1,2).

The rationale for antithyroid drug therapy, given to 5 patients, was symptomatic hyperthyroidism, but the therapy is unlikely to have been of benefit, given

the likely pathophysiology of the hyperthyroidism, namely thyroid injury sufficient to result in release of substantial amounts of T₄ and T₃ (and also thyroglobulin). That may be followed by transient subclinical or even overt hypothyroidism. Whether either occurred in these patients is not mentioned, but all eventually had normal thyroid function. Also not mentioned is whether the patients with hyperthyroidism had more neck pain or tenderness than the other patients.

In conclusion, not all symptoms that occur after parathyroid surgery are related

to disturbances in serum calcium or skeletal metabolism.

Robert D. Utiger, M.D.

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Children with hyperthyroidism tend to be tall and underweight, and continue to grow well when treated

Cassio A, Corrias A, Gualandi S, Tato L, Cesaretti G, Volta C, Weber G, Bona G, Cappa M, Bal M, Bellone J, Cicognani A. Influence of gender and pubertal stage at diagnosis on growth outcome in childhood thyrotoxicosis: results of a collaborative study. *Clin Endocrinol (Oxf)* 2006;64:53-7.

SUMMARY

Background Hyperthyroidism in children has been associated with accelerated growth, poor weight gain, and delayed puberty, but there has been little study of growth and development after diagnosis and initiation of therapy. In this study, the growth and pubertal development of children with hyperthyroidism was determined before and during long-term antithyroid drug therapy.

Methods The study subjects were 101 consecutive children (78 girls, 23 boys) with hyperthyroidism caused by Graves' disease seen at eight centers in north central Italy between 1975 and 1999. The girls were divided into three groups (prepubertal [Tanner breast stage 1], pubertal [Tanner breast stage ≥ 2], and postmenarchal), and the boys into two groups (prepubertal [testicular volume ≤ 3 ml] and pubertal [testicular volume > 3 ml]). All the children were treated with decreasing doses of methimazole or propylthiouracil, which was discontinued after the dose had been low for several months or hypothyroidism developed.

Height and weight were measured and pubertal stage was determined at base line, at 6-month intervals for 1 year, and yearly thereafter. Bone age was measured at base line. The growth, bone age, and body-mass index (BMI) data were expressed as standard deviation scores (SDS), defined as the deviation from the mean value for normal subjects of the same sex and age living in the same area. Predicted height was calculated as midparental height corrected for sex.

Results The mean duration of symptoms before diagnosis was 6 months (range, 1 to 36). It was similar in the prepubertal girls and boys (3 and 4 months, respectively), but considerably less in the pubertal girls than the pubertal boys (4 and 11 months, respectively). The mean height SDS and

bone age SDS were positive, and the body mass index SDS was negative, in the prepubertal and pubertal girls and boys (Table). In the postmenarchal girls, the mean height SDS was -0.24 and the body mass index was -0.52 .

Table. Mean Age, Height SDS, Bone Age SDS, and Body Mass Index SDS in Girls and Boys with Hyperthyroidism.

	Prepubertal		Pubertal	
	Girls (n=33)	Boys (n=15)	Girls (n=32)	Boys (n=8)
Age (yr)	7.6	9.3	11.9	13.5
Height SDS	0.67	0.35	0.31	1.42
Bone age SDS	1.03	1.02	0.81	0.70
Body-mass index SDS	-1.18	-1.95	-0.73	-1.32

The mean follow-up period was 5 years (range, 1 to 14), during which 82 children reached final height. Among 33 prepubertal girls and boys who reached final height, the height SDS remained positive; the final height SDS was 0.28 in the girls and 0.32 in the boys. Among 37 pubertal girls and boys, the height SDS decreased slightly in the girls, and it remained high in the boys. The girls' final height SDS was -0.23 , and that of the boys was 0.89. The final height was greater than the predicted height in all groups, ranging from 0.4 cm in the pubertal girls to 7.6 cm in the pubertal boys.

During treatment, the BMI SDS increased and then leveled off in the prepubertal and pubertal girls and boys. When final height was achieved, the BMI SDS was just below 0 in the prepubertal girls and boys, just above 0 in the pubertal girls, and approximately -0.65 in the pubertal boys.

Conclusion Height is increased and BMI is low in prepubertal and pubertal girls and boys with hyperthyroidism. Antithyroid drug therapy is accompanied by little change in growth rate, and therefore their final height may be greater than predicted.

COMMENTARY

The long-term adverse consequences of hypothyroidism on linear growth and bone maturation have been well documented, but the effects of hyperthyroidism are less clear. A strength of the study by Cassio et al. is the large, relatively homogeneous patient population, which permitted stratification by sex and pubertal status. Consistent with previous findings, final height was not affected in most groups. A somewhat surprising result was the increased final height in pubertal boys. This is contrary to the common expectation that final height

may be compromised in children with hyperthyroidism due to accelerated bony maturation. These boys had the highest height SDS of any subgroup at the time of diagnosis, probably because the duration of hyperthyroidism before diagnosis was considerably longer in them than in the other groups. Furthermore, they continued to grow more rapidly than normal during treatment, and their BMI remained low, suggestive of continuing hyperthyroidism. If this explanation is correct, similar findings would be expected in any child with severe hyperthyroidism, especially if longstanding or inadequately treated, regardless of sex

and pubertal status, analogous to the adverse effects of severe hypothyroidism on final height in children.

The sexual dimorphism in auxologic outcome in the pubertal but not prepubertal children and the less striking female:male ratio in the younger children are also noteworthy, and support a putative role for estrogen both in the propensity to develop Graves' hyperthyroidism and its effect on final height.

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Hyperthyroidism caused by Graves' disease has deleterious long-term effects on quality of life

Abraham-Nordling M, Topping O, Hamberger B, Lundell G, Tallstedt L, Calissendorff J, Wallin G. Graves' disease: a long-term quality-of-life follow up of patients randomized to treatment with antithyroid drugs, radioiodine, or surgery. *Thyroid* 2005;15:1279-86.

SUMMARY

Background Hyperthyroidism can result in disability and a substantial decrease in quality of life. The extent to which these changes are present after treatment is not known. In this study, patients who had hyperthyroidism were queried about their quality of life long after treatment.

Methods The study subjects were 145 patients with hyperthyroidism caused by Graves' disease and mild or no ophthalmopathy who were enrolled in a study of the effect of different antithyroid treatments on ophthalmopathy between 1983 and 1990. The original cohort consisted of 179 patients (149 women, 30 men); those aged 20 to 34 years were randomly assigned to antithyroid drug (methimazole) or surgical treatment, and those aged 35 to 55 years to drug, surgical, or radioiodine (I-131) treatment (hereafter referred to as the young and older groups, respectively).

In 2003, 14 to 21 years after the initiation of treatment, the patients completed two questionnaires. One questionnaire was the Short Form-36, a general questionnaire consisting of 36 items subdivided into a Physical Health Component score (the components are General Health, Bodily Pain, Role-Physical, and Physical Functioning) and a Mental Health Component score (Mental Health, Role-Emotional, Social Functioning, and Vitality). These eight items were each scored 0 (impairment) to 100 (no impairment), and the two main scores were weighted means. The other questionnaire consisted of 24 questions about recurrent hyperthyroidism, hypothyroidism, additional treatment, eye problems, co-morbidity, and the effects of the illness on well being, work and other activities, and family relationships. The results for each age group were compared between treatment subgroups, and the Short Form-36 scores were compared with those of normal subjects.

Results The 145 patients included 41 patients in the young group (22 treated surgically, 19 treated with drugs) and 104 patients in the older group (34 treated surgically, 36 treated with drugs, 34 treated with I-131).

In the young group, there were no differences in the Short Form-36 Physical Health Component or Mental Health Component scores or any of the subscores in the drug- and surgical-treatment subgroups. As compared with normal subjects, the Physical Health Component score and subscores were similar in both subgroups, but the Mental Health Component score and the Mental Health and Vitality subscores were significantly lower in both subgroups. In the older group, there were no differences in the Physical Health Component or Mental Health Component scores among the three treatment subgroups. As compared with normal subjects, the Mental Health Component score was lower in the drug-treatment subgroup, the General Health subscore was lower in the I-131-treatment subgroup, and the Vitality subscore was lower in all three subgroups.

The results of the 24-item questionnaire were similar in the five treatment subgroups. Nine to 37 percent of the patients reported having a relapse of hyperthyroidism, 3 to 9 percent had hypothyroidism, and 14 to 38 percent had some eye problems. The disease had affected career in 21 to 26 percent, family relationships in 6 to 33 percent, social relationships in 16 to 32 percent, and physical activities in 9 to 21 percent. From 23 to 38 percent reported that the disease made them feel gloomy and sad, and 32 to 53 percent were tired, but 63 to 74 percent reported feeling well.

Conclusion Patients with hyperthyroidism caused by Graves' disease, whether treated with an antithyroid drug, surgery, or I-131, have a long-term decrease in physical and mental quality of life.

COMMENTARY

This paper describes the second long-term follow-up study of this cohort (1). As noted above, the study was initiated to determine the effect of different treatments for Graves' hyperthyroidism on ophthalmopathy (2). The frequency of onset or worsening of ophthalmopathy was similar among the patients treated with drugs or surgery, but higher in those treated with I-131. In the first long-term study, done 4 to 10 years after treatment, 95 to 98 percent of the patients in the three treatment groups (age groups com-

bined) were satisfied with their treatment, although the overall rate of persistent or recurrent hyperthyroidism was high (40 percent, mostly in the patients treated with an antithyroid drug), and 16 to 20 percent did not think that they had recovered fully in one year.

Fourteen to 20 years later (this study), the Short Form-36 results (not used before) revealed virtually no between-group differences and only a few differences from normal subjects, but the responses to the more specific questions suggest that there may have been some lingering effects of

hyperthyroidism or its treatment.

Robert D. Utiger, M.D.

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Inhibition of tumor necrosis factor- α activity reduces periorbital inflammation in patients with Graves' ophthalmopathy

Paridaens D, van den Bosch WA, van der Loos TL, Krenning EP, van Hagen PM. The effect of etanercept on Graves' ophthalmopathy: a pilot study. *Eye* 2005;19:1286-9.

SUMMARY

Background Graves' ophthalmopathy is characterized by inflammation of the extraocular muscles and retroorbital fibroadipose tissue. The underlying causes of this inflammatory process are not known, but it is likely that proinflammatory cytokines are involved in both its initiation and perpetuation. Tumor necrosis factor- α (TNF- α) is one such cytokine, and inhibition of TNF- α activity with etanercept, a fusion protein consisting of the extracellular region of the cellular TNF- α receptor and the Fc component of immunoglobulin G, is an effective treatment for patients with several inflammatory disorders, notably rheumatoid arthritis. The efficacy of etanercept in patients with Graves' ophthalmopathy was evaluated in this study.

Methods The study was done in 10 patients (7 women, 3 men; age range, 39 to 59 years) with Graves' hyperthyroidism and ophthalmopathy. All had been treated with an antithyroid drug, and at base line had been euthyroid for at least two months. All had active ophthalmopathy, as defined by a Clinical Activity Score ≥ 3 (scored as 0 or 1 point for each of 10 items: orbital pain at rest or during eye movement, eyelid erythema or edema, conjunctival erythema or edema, caruncle swelling, >2 mm of proptosis, >1 -line decrease in visual acuity, and a decrease in ocular motility).

The patients were treated with 25 mg of etanercept given subcutaneously twice weekly for 12 weeks. At base line and at 6 and 12 weeks, the patients were evaluated using the Clinical Activity Score, the Ophthalmopathy Index (scored as 0 [absent] to 3 points [marked] each for soft-tissue

involvement of the eyes, proptosis, involvement of the extraocular muscles, corneal involvement, and sight loss), and a self-assessment questionnaire, and proptosis was measured by exophthalmometry.

Results All 10 patients completed the 12-week study. There was a decrease in the Clinical Activity Score and Ophthalmopathy Index, but not proptosis, during etanercept therapy (Table). At 12 weeks, the Clinical Activity Score decreased by 60 percent, and the Ophthalmopathy Index by 24 percent. The changes were mostly in eyelid and conjunctival erythema and edema.

Table. Mean (Range) Clinical Activity Score, Ophthalmopathy Index, and Proptosis during Etanercept Therapy in Patients with Graves' Ophthalmopathy.

	Base Line	6 Weeks	12 Weeks
Clinical Activity Score	4.0 (3-6)	2.6 (0-6)	1.6 (0-4)
Ophthalmopathy Index	5.8 (3-10)	4.8 (4-7)	4.4 (3-7)
Proptosis (mm)	22 (15-30)	22 (15-30)	22 (15-28)

At base line, six patients had diplopia, which improved in three. Visual acuity did not change in any patient. All patients reported some subjective improvement. Three patients had an increase in periorbital inflammation 2 to 6 weeks after treatment was stopped. The injections were tolerated well, and there were no late adverse effects during a mean follow-up period of 18 months.

Conclusion Treatment with etanercept, an inhibitor of TNF- α activity, for 12 weeks decreases eyelid and conjunctival inflammation, but not proptosis, in patients with Graves' ophthalmopathy.

COMMENTARY

Graves' ophthalmopathy is a debilitating condition for which therapeutic options are limited, and new approaches to therapy are badly needed. Indeed, there is little to offer some patients beyond reassurance that the natural history is one of gradual improvement with time. It is this disease course, however, that complicates studies of therapy; without a control group, any results are very difficult to interpret.

Recent studies have implicated both Th1-type and macrophage-derived cytokines in the pathogenesis of Graves' ophthalmopathy (1). On this basis, agents that block the action of tumor necrosis factor (etanercept, infliximab, or adalimumab) or interleukin-1 (anakinra) or the

activation of T cells (alefacept) are attractive candidates for therapy. In addition, given the likely role of thyrotropin-receptor and other antibodies in the pathogenesis of ophthalmopathy, agents that block the maturation or activation of B cells (retuximab) may hold promise.

In this small pilot study of etanercept, the mean Clinical Activity Score decreased by 60 percent and the Ophthalmopathy Index decreased by 24 percent after 12 weeks of treatment. The authors concluded that the study "strongly suggests" that etanercept may ameliorate the clinical manifestations of Graves' ophthalmopathy, especially eyelid and conjunctival erythema and edema. This assertion seems an overstatement, given the lack of a control group. Nonetheless, these preliminary results, coupled with

the increasing evidence for the role of cytokines in the pathogenesis of ophthalmopathy, should lead to initiation of the controlled trials of etanercept and other anticytokine agents that will be needed to determine if patients with Graves' ophthalmopathy are to benefit from the new insights into its pathogenesis.

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People with subclinical hypothyroidism do not have neuropsychologic abnormalities or symptoms of hypothyroidism

Jorde R, Waterloo K, Storhaug H, Nytnes A, Sundsfjord J, Jenssen TG. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J Clin Endocrinol Metab* 2006;91:145-53.

SUMMARY

Background The presence of subclinical hypothyroidism (high serum thyrotropin [TSH] and normal free thyroxine [T₄] concentrations) is indicative of a small decrease in thyroid secretion, but whether the decrease results in any symptoms or disability is debated, as is the effect of T₄ therapy. In this study, neuropsychologic function, symptoms of hypothyroidism, and the effects of T₄ therapy were evaluated in subjects with subclinical hypothyroidism (or high normal serum TSH values) identified in a community survey.

Methods In 2001, 7954 subjects aged 30 years or older living in Tromsø, Norway, completed a health questionnaire and had measurements of serum TSH. After exclusions for illness, thyroid hormone therapy, unwillingness to participate in further studies, and abnormal serum free T₄ concentrations, there were 89 subjects with serum TSH concentrations of 3.5 to 10 mU/L on two occasions (normal range, 0.2 to 4.2).

These 89 subjects and 154 age- and sex-matched subjects with serum TSH values of 0.5 to 3.4 mU/L were given seven tests of cognitive function, two tests of emotional status, and a 19-item hypothyroid symptom questionnaire. The tests of cognitive function included tests of attention, memory, psychomotor/cognitive speed, and intelligence. The tests of emotional status were the Beck Depression Inventory and the General Health Questionnaire 30, which has subscores for anxiety, depression, social dysfunction, and related topics.

Sixty-nine subjects with subclinical hypothyroidism were randomly assigned to receive T₄ or placebo for 12 months, after which they were given the same tests.

Results The 89 subjects with subclinical hypothyroidism included 44 women and 45 men (mean age, 62 years), with a mean serum TSH value of 5.7 mU/L. The 154 control subjects included 82 women and 72 men (mean age, 61 years); their mean serum TSH value was 1.8 mU/L.

There were no differences in the scores for the tests of cognitive function between the subjects with subclinical hypothyroidism and the control subjects. The scores for the Beck Depression Inventory were similar in the two groups, and the subjects with subclinical hypothyroidism had more favorable scores on the General Health Questionnaire-30 (P<0.01). The responses to the hypothyroid symptom questionnaire also were similar in the two groups. (Thirty-eight of the subjects with subclinical hypothyroidism [43 percent] had serum TSH values between 5.0 and 10 mU/L. Their results were similar to those in the 89 subjects with subclinical hypothyroidism as defined above.)

In the treatment study, 36 subjects were assigned to the T₄ group and 33 to the placebo group. At study end, the mean dose of T₄ was 110 µg daily; the mean serum TSH value in the T₄-therapy group was 1.5 mU/L, and it was 5.4 mU/L in the placebo group. There were no differences in the scores for any of the tests of cognitive function and emotional status or the hypothyroid symptom scores between the groups at base line, and there were no changes in the scores or changes in hypothyroid symptoms at the end of the 12-month treatment period.

Conclusion Subjects with mild subclinical hypothyroidism have no abnormalities in cognitive function or emotional status or symptoms of hypothyroidism, and treatment with T₄ results in no changes in any of these characteristics.

COMMENTARY

This study provides more evidence that subjects with subclinical hypothyroidism, at least those with mild subclinical hypothyroidism (serum TSH values ≤10 mU/L), have no symptoms or other disabilities, and that T₄ therapy has no benefit. The strengths of the study include recruitment from the community, stable thyroid function (two similar serum TSH values, but at an unstated interval), and the use of many tests and questionnaires. However, the definition of subclinical hypothyroidism was unusual, because it included subjects with serum TSH values within the normal range. Indeed, they accounted for the

majority (57 percent) of the subjects in that group. Although the results in the subjects whose serum TSH values were 3.5 to 4.2 mU/L (the latter value being the upper limit of normal) and those whose serum TSH values were 3.5 to 4.9 mU/L (the cut-off used to subdivide the subclinical-hypothyroidism group) were not given, they must have been similar to the results in both the group as a whole and the subjects with serum TSH values of 5.0 to 10 mU/L.

The expansion of the definition of subclinical hypothyroidism to include subjects with serum TSH values within the normal range is not explained, but may have been done to address the debate about lowering the upper limit of

the normal range for serum TSH (1,2). The results of both the cross-sectional study and the T₄-treatment study provide no support for that proposal.

Robert D. Utiger, M.D.

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Consumptive hypothyroidism can be caused by a fibrous tumor

Ruppe MD, Huang SA, Jan de Beur SM. Consumptive hypothyroidism caused by paraneoplastic production of type 3 iodothyronine deiodinase. *Thyroid* 2005;15:1369-72.

SUMMARY

Background Consumptive hypothyroidism is hypothyroidism resulting from rapid degradation of thyroxine (T_4) and triiodothyronine (T_3). The rapid degradation is caused by an increase in the activity of type 3 iodothyronine deiodinase, which catalyzes the conversion of T_4 to 3,3',5'-triiodothyronine (reverse T_3) and T_3 to 3,3'-diiodothyronine (T_2), both of which are biologically inactive. To date, all patients with consumptive hypothyroidism have had large vascular tumors; they included infants with hemangiomas and an adult with a hemangioendothelioma. This report describes an adult with consumptive hypothyroidism caused by a large fibrous tumor.

Case Report The patient was a 54-year-old man with a 13-year history of hypothyroidism that was increasingly difficult to treat. From mid-1999 to early 2001, while taking T_4 in doses of 200 to 1000 μg daily (usually 600 to 800 μg daily), he had normal serum free T_4 and low free T_3 concentrations but high serum thyrotropin (TSH) concentrations (10 to 100 mU/L); his clinical status during this interval was not described. Early in 2001 he noted increasing abdominal enlargement, confirmed by physical examination. CT imaging revealed a 28 x 16 cm mass that extended into his pelvis. The mass was resected in May, 2001; pathologic examination revealed a malignant fibrous tumor.

While taking 800 μg of T_4 daily just before surgery, his serum free T_4 concentration was 1.7 ng/dl (22 pmol/L) and his serum TSH concentration was 20 mU/L. That dose was continued after surgery. Within a week he had onset of symptoms of hyperthyroidism (palpitations, heat intolerance). His serum free T_4 and free T_3 concentrations were high (3.1 ng/dl [40 pmol/L] and 0.5 ng/dl [7.7 pmol/L], respectively), and his serum TSH concentration was low (0.09 mU/L). The dose of T_4 was reduced to 175 μg daily, after which his serum free T_4 and TSH concentrations were normal, including when last measured 9 to 12 months later.

RNA was extracted from the tumor, placenta (the tissue that contains the most type 3 deiodinase activity), and liver (a type 3 deiodinase-poor tissue) and reverse transcribed to form complementary DNA. Type 3 deiodinase messenger RNA was detected in the tumor and placenta, but not liver; the tumor content was 1.3 times that of the placenta. Immunoblot analysis of extracts of these tissues using a polyclonal anti-type 3 deiodinase antibody revealed type 3 deiodinase protein in the tumor and placenta, but not liver. Tumor type 3 deiodinase activity (V_{max} , 74 fmol of T_3 deiodinated/min/mg protein) was higher than that in placenta (V_{max} , 45 fmol of T_3 deiodinated/min/mg protein).

Conclusion Tumors composed largely of fibrous tissue may cause consumptive hypothyroidism.

COMMENTARY

For hypothyroidism to occur as a result of excessive deiodination of T_4 and T_3 , the deiodination rate has to exceed the capacity of the thyrotroph cells of the pituitary to increase TSH secretion and then that of the thyroid to increase T_4 and T_3 secretion to compensate for the excess deiodination. That capacity is large. TSH secretion can increase sufficiently to raise serum TSH concentrations to 100 mU/L or higher in patients with hypothyroidism, and even small increases in TSH secretion within the normal range result in several fold increases in T_4 and T_3 secretion and serum T_4 and T_3 concentrations in patients with TSH-secreting pituitary tumors or generalized thyroid hormone resistance. Therefore, compensation for excessive deiodination of T_4 and T_3 should be complete, unless the increase in the rate of deiodination is very large. Some thyroid enlargement also would be expected. In addition, an increase in iodine intake would be needed to sustain the high level of secretion of T_4 and T_3 .

This man is said to have had hypothyroidism for 13 years. It is likely that the tumor was present from the beginning and that it grew very slowly (it is described as a malignant fibrous tumor, but the features of malignancy are not described). The findings at the time of diagnosis of hypothyroidism and during most of those years also are not described. Did he have a goiter? He apparently was well for years while taking a moderate dose of T_4 , but he may not have had normal serum TSH concentrations. Subsequently, doses of T_4 8 to 10 times the daily T_4 secretion rate were not adequate. The tumor content of type 3 deiodinase was high. Its location (vascular or fibrous tissue) was not determined, but there is no reason to doubt that it was active in vivo. In that regard, a key finding in patients with consumptive hypothyroidism is a high serum reverse T_3 concentration, which was not measured in this man. It is also possible that the large bulk of the tumor in his abdomen decreased T_4 absorption.

How common is consumptive hypothyroidism? Only one case has been

reported in an adult, a woman who had a hepatic hemangioendothelioma (1). But it may not be rare, only unrecognized. Even if type 3 deiodinase is restricted to blood vessels, many tumors have abnormal vessels. Given the capacity of the pituitary-thyroid system to increase T_4 and T_3 secretion, it is likely that compensation for a several fold increase in the rate of T_4 and T_3 deiodination would be complete, the patient having not only normal serum free T_4 and free T_3 concentrations, but also normal or only minimally elevated serum TSH concentrations (and no obvious thyroid enlargement); the disorder would be detected only if serum reverse T_3 was measured.

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Hypopituitarism can occur after radiation therapy in patients with brain tumors

Agha A, Sherlock M, Brennan S, O'Connor SA, O'Sullivan E, Rogers B, Faul C, Rawluk D, Tormey W, Thompson CJ. Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. *J Clin Endocrinol Metab* 2005;90:6355-60.

SUMMARY

Background External-beam radiation directed to the region of the hypothalamus and pituitary gland is a well-known cause of hypopituitarism. Whether radiation given as treatment for primary brain tumors also causes hypopituitarism is less clear. In this cross-sectional study, hypothalamic-pituitary function was evaluated in adults with brain tumors after treatment.

Methods The study subjects were 76 patients with a brain tumor; 56 had been treated with external-beam radiation one or more years earlier and 20 had not. The radiation group consisted of 28 women and 28 men; their mean age was 33 years at the time of radiation therapy and 39 years when studied. The mean effective radiation dose was 54 Gy (range, 4 to 97). The no-radiation group consisted of 8 women and 12 men; their mean age when studied was 36 years. Patients with a grade III or IV astrocytoma and those who had taken a glucocorticoid within the preceding six months were excluded. Most patients in both groups had a low-grade glioma, but a few had a meningioma or other tumor. The tumor had been surgically resected in approximately two-thirds of the patients in both groups and biopsied in nearly all of the others.

Growth hormone (GH) deficiency was defined as a peak serum growth hormone value <5 µg/L in response to insulin-induced hypoglycemia or both glucagon and arginine. Gonadotropin (GSH) deficiency was defined as oligomenorrhea or amenorrhea and low serum estradiol and normal or low serum gonadotropin values in premenopausal women, inappropriately low serum gonadotropin values in postmenopausal women, and low serum testosterone and normal or low serum gonadotropin values in men. Corticotropin (ACTH) deficiency was defined as a peak serum cortisol <18 µg/dl (500 nmol/L) in

response to hypoglycemia or corticotropin. Thyrotropin (TSH) deficiency was defined as a low serum free thyroxine and a low or normal thyrotropin value.

Results The mean interval between therapy and hormonal testing in the radiation group was 3.2 years (range, 1 to 12.5). Among the patients in the radiation group, 23 (41 percent) had one or more pituitary hormone deficiencies. Nine (16 percent) had one deficiency and 14 (25 percent) had multiple deficiencies, including 4 (7 percent) who had panhypopituitarism. The frequency of different deficiencies and of hyperprolactinemia in these patients and in the patients not treated with radiation is shown in the Table.

	Radiation Therapy (n=56)	No Radiation Therapy (n=20)
Panhypopituitarism	4 (7%)	0
GH, ACTH, and TSH	1 (2%)	0
GH, ACTH, and GSH	4 (7%)	0
GH and ACTH	1 (2%)	0
GH and GSH	4 (7%)	0
GH	4 (7%)	1 (5%)
ACTH	2 (4%)	0
GSH	3 (5%)	0
Hyperprolactinemia*	18 (32%)	0

*The values were ≤2 times the upper limit of normal in 8 patients and >2 times the upper limit of normal in 10.

Overall; 18 patients (32 percent) had GH deficiency, 15 (27 percent) GSH deficiency, 12 (21 percent) ACTH deficiency, and 5 (9 percent) TSH deficiency. Any pituitary hormone deficiency was associated with radiation dose and a longer time interval after radiation therapy. Hyperprolactinemia was associated only with radiation dose.

Conclusion Patients with brain tumors who are treated with external-beam radiation are at risk for hypopituitarism, especially those who are treated with high doses and those who survive for many years.

COMMENTARY

It is reasonable to attribute the changes to radiation, given the results in the no-radiation group and the fact that cranial radiation in patients with nasopharyngeal tumors can cause hypopituitarism (1). The radiation-induced injury is thought to be primarily in the hypothalamus, rather than the pituitary gland. However, the evidence supporting this conclusion is based largely on the results of tests with hypothalamic-releasing hormones, which do not distinguish well between hypothalamic hormone and

pituitary hormone deficiencies.

What are the clinical consequences of the deficiencies detected in studies like this? The patients were not queried about symptoms of pituitary hormone deficiencies, excepting young women who were asked about their menstrual cycles, and nothing is said about treatment of any pituitary hormone deficiencies that were detected. Whether symptomatic or not, it would seem prudent to recommend treatment for any young woman with oligomenorrhea or amenorrhea, any man with a low serum testosterone concentration, and anyone with a low serum free

thyroxine or cortisol concentration.

However, whether growth hormone also should be recommended is controversial.

Robert D. Utiger, M.D.

Reference

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Thyroid biopsies are suspicious for carcinoma more often in patients with thyroid nodules who have high serum antithyroid antibody values

Boi F, Lai ML, Marziani B, Minerba L, Faa G, Mariotti S. High prevalence of suspicious cytology in thyroid nodules associated with positive thyroid antibodies. *Eur J Endocrinol* 2005;153:637-42.

SUMMARY

Background Patients with thyroid carcinoma are more likely to have high serum antithyroid antibody concentrations than normal subjects, but whether high concentrations indicate that a thyroid nodule is likely to be a carcinoma is not known. In this study, the relationships between serum antithyroid antibody concentrations and the results of biopsy of thyroid nodules and histology of the nodules that were excised were studied.

Methods During a 2-year interval, 590 consecutive patients (533 women, 57 men; age range, 18 to 91 years) with a solitary or dominant thyroid nodule underwent fine-needle aspiration biopsy and had measurements of serum antithyroid peroxidase antibodies (normal, <20 U/ml) and antithyroglobulin antibodies (normal, none detected). The biopsies were done with ultrasound guidance, and the results were divided into three groups. Biopsies suggestive of a colloid nodule (colloid and macrophages with few follicular cells); those with thyroid follicular cells with normal nuclei; those containing follicular cells, some with oncocytic changes, and lymphocytes (cytologic criteria for Hashimoto's thyroiditis); and those that were inadequate (number not given separately) were designated benign/inadequate. Biopsies containing pleomorphic follicular cells in a microfollicular pattern and little colloid were designated follicular tumor, and those containing cells with the nuclear features of papillary carcinoma (crowded large polymorphic nuclei, with nuclear grooves and pseudo-inclusions) were designated suspicious/definite for carcinoma. Whether the cytopathologist was aware of the serologic results when interpreting the biopsies is not stated.

Results Among the 590 patients, 197 (33 percent) had a high serum concentration of antithyroid peroxidase or

antithyroglobulin antibodies and 393 (67 percent) did not. As compared with the patients with normal serum antithyroid antibody values, relatively more patients with high serum antithyroid antibody values had biopsies that revealed a follicular tumor (29 vs. 21 percent) or were suspicious/definite for carcinoma (19 vs. 9 percent) (Table). High serum antithyroid antibody values were more common in women than in men (37 vs. 13 percent). Among the patients in whom the biopsy was suspicious/definite for carcinoma, the odds ratio for a high serum antithyroid antibody value was 2.3 ($P < 0.01$).

Cytology Group	Serum Antithyroid Antibody Value	
	High (n=197)	Normal (n=393)
Benign/inadequate	103 (52%)*	273 (69%)
Follicular tumor	57 (29%)*	84 (21%)
Suspicious/definite for carcinoma	37 (19%)*	36 (9%)

* $P < 0.01$, as compared with the normal serum antibody group.

One hundred six patients have undergone surgery. The nodule was a carcinoma in none of the 14 patients from the benign-biopsy group, 6 of the 31 patients (19 percent) from the follicular-tumor group, and 54 of the 61 patients in the suspicious/definite-for-carcinoma group (88 percent). The 106 surgically treated patients included 42 with high serum antithyroid antibody values, of whom 27 (64 percent) had a carcinoma, and 64 with normal serum antithyroid antibody values, of whom 33 (52 percent) had a carcinoma (difference not statistically significant).

Conclusion In patients who have a thyroid nodule, the results of biopsy are more likely to indicate the presence of a follicular tumor or be suspicious/definite for carcinoma in those with high serum antithyroid antibody concentrations than in those with normal concentrations.

COMMENTARY

The finding of an association between high serum antithyroid antibody concentrations and a biopsy diagnosis of follicular tumor or suspicious/definite for carcinoma in patients with thyroid nodules should not be taken as evidence that thyroid carcinoma is more common in patients with chronic autoimmune thyroiditis. In long-term studies of patients with chronic autoimmune thyroiditis, the incidence of thyroid carcinoma was not increased (1). In this study, relatively few patients in the two biopsy groups likely to have carcinoma were operated on, and therefore the true relationship between

high serum antithyroid antibody values and thyroid carcinoma in the cohort is not known. The results do complement the observations that patients with thyroid carcinoma are more likely to have high serum antithyroid antibody values than are normal subjects, but that does not prove a relationship with chronic autoimmune thyroiditis. What are lacking are the results of simultaneous histologic studies of the thyroid and measurements of serum antithyroid antibodies in large groups of patients with thyroid carcinoma. It is likely that in some patients with thyroid carcinoma the high serum antibody concentrations are a response to tumor antigens, rather than coexisting

chronic autoimmune thyroiditis.

In any event, it seems obvious that, among patients with thyroid nodules, measurements of serum antithyroid antibodies cannot be used to identify those whose nodule(s) should be biopsied.

Robert D. Utiger, M.D.

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Positron-emission tomography using fluorodeoxyglucose may distinguish between benign thyroid nodules and thyroid carcinomas

Mitchell JC, Grant F, Evenson AR, Parker JA, Hasselgren PO, Parangi S. Preoperative evaluation of thyroid nodules with 18-FDG-PET/CT. *Surgery* 2005;138:1166-75.

SUMMARY

Background Positron-emission imaging with 18-fluorodeoxyglucose (FDG-PET), especially when combined with computed tomography (FDG-PET/CT), has proven useful in identifying sites of persistent or recurrent tumor in patients with carcinoma of the thyroid. In general, carcinomas take up more FDG than do benign tumors. This study assessed the value of FDG-PET/CT for the preoperative detection of thyroid carcinoma.

Methods FDG-PET/CT imaging was done in 31 patients (24 women, 7 men; mean age, 49 years), with 48 thyroid nodules, who had been scheduled for surgery.

The FDG was given intravenously in a dose of 20 mCi (740 MBq) after the patients had fasted for at least six hours. The scans were done one hour later. The relative avidity of nodules for FDG was measured as the maximum standard uptake value normalized for body weight (SUV).

Results Seventeen patients had a solitary nodule and 14 had multiple nodules. Based on the results of fine-needle-aspiration cytology, 10 nodules were suspicious for carcinoma, 24 were follicular tumors, and 1 was benign; 13 were not aspirated. The indication for surgery was the biopsy result in 28 patients, local symptoms in 2, and increasing nodule size in 1.

Among the 48 nodules, 15 were carcinomas and 33 were benign. The 15 carcinomas included 12 papillary carcinomas, 1 Hurthle-cell carcinoma, 1 anaplastic carcinoma, and 1 renal-cell carcinoma that had metastasized to the thyroid. The 33 benign nodules included 13 follicular adenomas, 8 Hurthle-cell adenomas, and 12 hyperplastic nodules.

The SUV for the 15 carcinomas ranged from 0.0 to 15.5 (mean, 6.5). The values for the benign nodules ranged from 0.0 to 5.1 (mean, 1.1) (Table).

	Mean SUV (Range)
Adenoma (n=21)	2.4 (0.0-5.1)
Follicular (n=13)	1.8 (0.0-4.4)
Hurthle-cell (n=8)	3.3 (0.0-9.8)
Hyperplastic nodule (n=12)	1.1 (0.0-5.1)
Carcinoma (n=15)	6.5 (0.0-15.5)
Papillary (n=12)	6.2 (0.0-15.5)
Hurthle-cell (n=1)	10.0
Other (n=2)	2.3, 5.8

The SUV was <5.0 in 30 of the 33 benign nodules (91 percent) and 7 of the 15 carcinomas (47 percent). Among the latter, 5 were papillary carcinomas <1 cm in diameter, 1 was a 3.5-cm papillary carcinoma, and 1 was a metastasis of a renal carcinoma. The SUV was ≥5.0 in 3 of the 33 benign nodules (9 percent), 2 Hurthle-cell adenomas and 1 hyperplastic nodule, and 8 carcinomas (53 percent). The positive predictive value for carcinoma of a SUV value ≥5.0 was 73 percent and the negative predictive value was 81 percent.

Among the 24 follicular tumors diagnosed by cytology, 23 were benign and 1 was a papillary carcinoma. The SUV was ≥5.0 in 2 of the benign nodules (a Hurthle-cell adenoma and a hyperplastic nodule), and it was 2.3 in the carcinoma.

Conclusion In patients with thyroid nodules, preoperative FDG-PET/CT imaging can help in distinguishing between benign nodules, including follicular and Hurthle-cell adenomas, and carcinomas.

COMMENTARY

FDG-PET/CT has probably become the preferred imaging procedure for patients with thyroid carcinoma who have evidence of recurrent tumor, as manifested by high basal or stimulated serum thyroglobulin concentrations, but in whom ultrasonography of the neck and radioiodine imaging reveal no tumor. Tumor detected in this way is not, however, readily treatable, which should dampen enthusiasm for the test.

Might FDG-PET/CT have value as a diagnostic test to distinguish benign thyroid nodules and carcinoma? That seems unlikely, given the results reported here and the high cost of the test.

Unfortunately, simple tests, such as measurements of serum thyroglobulin or ultrasonography alone, do not reliably distinguish between benign nodules and carcinoma (1,2). Fine-needle aspiration, with evaluation of the cytology of the aspirated cells, does, but to a limited extent. This procedure basically yields five diagnoses: benign thyroid follicular cells; papillary carcinoma, or suspicious for papillary carcinoma (really the same thing); follicular tumor, including Hurthle-cell tumor (sometimes called indeterminate); medullary carcinoma; and too few cells for diagnosis.

FDG-PET/CT does not provide this level of precision. It might prove useful in distinguishing follicular adenomas and follicular carcinomas. But that is speculation; no patient studied by Mitchell et al. had a follicular carcinoma.

Robert D. Utiger, M.D.

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Hurthle-cell carcinomas of the thyroid may have characteristics of papillary carcinomas or follicular carcinomas

Maxwell EL, Palme CE, Freeman J. Hurthle cell tumors: applying molecular markers to define a new management algorithm. *Arch Otolaryngol Head Neck Surg* 2006;132:54-8.

SUMMARY

Background Hurthle cells, also called oncocytic cells, are thyroid follicular cells that have a characteristic granular cytoplasm, due to the presence of many mitochondria. Some thyroid adenomas and carcinomas are composed largely of Hurthle cells, and these cells are also found in many non-neoplastic thyroid disorders. Among Hurthle-cell carcinomas, some have the histologic appearance, growth pattern, and clinical characteristics of follicular carcinomas. Others have the characteristics of papillary carcinomas, including the *Ret/PTC* gene rearrangements that are found in many papillary carcinomas. In this retrospective study, the course of 45 patients with Hurthle-cell carcinoma was determined, and a management scheme based on the histology of the tumor and expression of *Ret/PTC* in tumor cells was proposed.

Methods Forty-five patients (34 women, 11 men; age range, 32 to 92 years) with Hurthle-cell carcinoma were identified from among a cohort of 661 patients with differentiated thyroid carcinoma (7 percent) on the basis of histologic features and the presence of capsular or vascular invasion or distant metastases. The tumors ranged from 0.5 to 8.0 cm in size (median, 2.5). They were multifocal in 15 patients (33 percent), and 25 (56 percent) had regional lymph node metastases, suggestive of papillary carcinoma. Extracapsular invasion was seen in 9 patients (20 percent) and vascular invasion in 7 (16 percent), suggestive of follicular carcinoma. Treatment consisted of total thyroidectomy in 41 patients (91 percent), subtotal thyroidectomy in 4 (9 percent), at least one dose of radioiodine in 39 (87 percent), and external-beam radiation therapy in 2 (4 percent).

Results At the time of this study, 40 patients (89 percent) were alive with no evidence of disease, 3 had recurrent car-

cinoma, and 2 had died of carcinoma. The median duration of follow-up was 94 months (range, 2 to 261). The overall disease-specific survival was 96 percent at five years. Among the patients with vascular invasion, the five-year disease-free rate and the five-year disease-specific survival rate were both 87 percent. Tumor size, extracapsular invasion, multifocal tumor, and regional lymph node metastases were not associated with recurrence, nor were extent of surgery and radioiodine therapy.

In a separate study, 34 of 50 Hurthle-cell adenomas and carcinomas (68 percent), as defined by histology, expressed the *Ret/PTC* oncogene, indicative of papillary-carcinoma lineage, independent of their histologic appearance.

These clinical and molecular characteristics were combined in a proposal for management of patients with thyroid nodules in whom fine-needle aspiration reveals Hurthle cells, starting with thyroid lobectomy (Table).

Table. Hurthle-Cell Nodule—Thyroid Lobectomy, with Frozen-Section Analysis of the Nodule.	
1.	If vascular or capsular invasion is seen, total thyroidectomy should be done (Hurthle-cell carcinoma, follicular subtype).
2.	If the cytologic features of papillary carcinoma are seen, total thyroidectomy and lymph node dissection should be done (Hurthle-cell carcinoma, papillary subtype).
3.	If there is no evidence of carcinoma, stop, and await the results of analysis of permanent sections. <ol style="list-style-type: none"> a. If this analysis reveals the tumor to be invasive or to have the cytologic features of papillary carcinoma, do completion thyroidectomy. b. If not, perform analysis for <i>Ret/PTC</i>. <ol style="list-style-type: none"> i. If positive, do completion thyroidectomy. ii. If not, consider the nodule a Hurthle-cell adenoma.

Conclusion Some Hurthle-cell carcinomas of the thyroid have cytologic, molecular, and clinical characteristics of papillary carcinomas, whereas others have the histologic and clinical characteristics of follicular carcinomas.

COMMENTARY

Hurthle-cell tumors, by arbitrary definition, are tumors composed of ≥ 75 percent Hurthle cells. Hurthle-cell carcinomas have generally been thought to be a variant form of follicular carcinoma, and they are determined to be carcinomas by the same histologic criteria used to define follicular carcinomas, namely capsular or vascular invasion. However, some Hurthle-cell carcinomas behave clinically like papillary carcinomas, in that they are multifocal and spread to regional lymph nodes. And some carry and express one of the several forms of the *Ret/PTC* oncogene that are present in a substan-

tial proportion of classical papillary carcinomas (1,2). So, also, do some tumors considered histologically to be Hurthle-cell adenomas. In other words, some Hurthle-cell carcinomas (and adenomas) are papillary carcinomas at the molecular level, which may explain their clinical behavior.

As for determining the nature of a Hurthle-cell tumor detected by biopsy, the optimal study is probably to test for the *Ret/PTC* oncogene in the biopsy specimen, rather than relying on analysis of frozen sections and testing for the oncogene only after the tumor has been surgically resected.

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Robert D. Utiger, M.D.

Ultrasonography of the neck is the most sensitive test for detection of recurrent tumor in patients with a papillary microcarcinoma

Torlontano M, Crocetti U, Augello G, D'Aloiso L, Bonfitto N, Varraso A, Dicembrino F, Modoni S, Frusciante V, Di Giorgio A, Bruno R, Filetti S, Trischitta V. Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole-body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid microcarcinoma who have not undergone radioiodine therapy. *J Clin Endocrinol Metab* 2006;91:60-3.

SUMMARY

Background Papillary microcarcinomas may be detected by physical examination or an imaging study, or at the time of surgery for other thyroid lesions. The prognosis of patients with a microcarcinoma is excellent, and therefore they are treated less aggressively and studied less often post-operatively than are patients with larger tumors, but a few do have recurrences. In this study, the value of several tests for detecting recurrent tumor was evaluated in patients with papillary microcarcinoma.

Methods The study subjects were 80 patients (69 women, 11 men; age range, 24 to 72 years) with a ≤ 1 cm papillary carcinoma. Eleven patients had a solitary thyroid nodule, biopsy of which was positive for papillary carcinoma. The other 69 patients had a multinodular goiter, and the carcinoma was detected incidentally at the time of surgery. The mean (\pm SD) tumor size was 0.6 ± 0.2 cm. All the patients underwent near-total thyroidectomy, and those with solitary nodules underwent central neck dissection as well. They then were treated with replacement doses of thyroxine. Patients with multifocal tumors or high serum antithyroglobulin antibody concentrations were excluded.

The follow-up studies were done 6 to 12 months after surgery. They included clinical examination, ultrasonography of the neck, and whole-body I-131 scan and measurements of serum thyroglobulin (Tg) before and after intramuscular administration of 0.9-mg doses of recombinant thyrotropin (TSH), given on two successive days. The I-131 was given 24 hours after the last injection, and the scan and serum measurements were done 48 hours later. Thyroxine therapy was not stopped.

Results Basal serum Tg concentrations were ≤ 1 ng/ml in 76 patients (95 percent) and >1 ng/ml in 4 (5 percent). After TSH administration, serum Tg concentrations were ≤ 1 ng/ml in 45 patients (56 percent) and >1 ng/ml in 35 (44 percent).

Ultrasonography of the neck revealed findings suspicious for lymph-node metastases, confirmed by biopsy, in 3 patients (4 percent). Two of these patients had serum Tg concentrations ≤ 1 ng/ml after TSH stimulation.

The 48-hour uptake of I-131 in the thyroid bed ranged from 0.1 to 10.2 percent (mean, 3.1); there was no extrathyroidal uptake in any patient. Among the 77 patients with no lymph-node metastases, 14 (18 percent) had thyroid-bed uptake values ≤ 0.5 percent; all had TSH-stimulated serum Tg concentrations ≤ 1 ng/ml. In contrast, 33 of the 63 patients (52 percent) who had thyroid-bed uptake values >0.5 percent had TSH-stimulated serum Tg concentrations >1 ng/ml. There was a strong positive correlation between TSH-stimulated serum Tg concentrations and thyroid-bed uptake ($P < 0.01$).

Seventy-four patients were followed for 10 to 72 months (mean, 32) after surgery. Follow-up ultrasound studies revealed no evidence of recurrent tumor in any of these patients. The 4 patients who initially had basal serum Tg concentrations >1 ng/ml had basal serum Tg concentrations ≤ 1 ng/ml during follow-up.

Conclusion Among patients with papillary microcarcinoma, ultrasonography of the neck is a more sensitive test for detecting recurrence than is either measurement of serum Tg or thyroid scintigraphy after TSH stimulation.

COMMENTARY

Papillary microcarcinomas are usually defined as papillary carcinomas ≤ 1 cm, ≤ 1.5 cm, or even ≤ 2 cm in longest dimension, the latter after the cancer-staging groups changed the definition of a stage 1 thyroid carcinoma from ≤ 1 cm to ≤ 2 cm several years ago. A lower limit is rarely defined, but presumably the tumor must be visible to the naked eye, thus excluding those detected only in histologic sections of thyroid tissue.

The prognosis of patients with a papillary microcarcinoma is excellent, no matter how the carcinoma is detected or how the patient is treated. That includes

patients in whom the microcarcinoma is found at the time of thyroid lobectomy for a nodule that proved to be benign, and in whom completion thyroidectomy is not done. Nonetheless, some patients later have nodal or, rarely, distant metastases, and therefore some surveillance is indicated. That should consist of occasional ultrasonography of the neck and measurements of serum Tg. It is a little harder to interpret the results of measurements of serum Tg in patients who have residual normal thyroid tissue, for example in patients who had a thyroid lobectomy and do not need thyroxine therapy for iatrogenic hypothyroidism (whether they should be treated to

reduce TSH secretion anyway can be debated). If serum TSH and Tg concentrations are normal, and stay normal, tumor recurrence is unlikely, and if the patients are treated with thyroxine the serum Tg values should be persistently a little low (1).

Robert D. Utiger, M.D.

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Thyroid function during pregnancy is normal in women with a history of Graves' disease who are in remission

Luton D, Le Gac I, Noel M, Guibourdenche J, Polak M. Thyroid function during pregnancy in women with past Graves' disease. *BJOG* 2005;112:1565-7.

SUMMARY

Background Hyperthyroidism caused by Graves' disease is common in young women. Some of them have a long-term remission when treated with an antithyroid drug, and later may become pregnant, which in normal women results in substantial changes in pituitary–thyroid function. This study was done to determine the changes in pituitary–thyroid function in pregnant women with Graves' hyperthyroidism who were in remission.

Methods The study subjects were 34 pregnant women with a history of Graves' hyperthyroidism in remission and 102 pregnant women with no history of thyroid disease. The diagnosis of Graves' hyperthyroidism was based on clinical and laboratory evidence of hyperthyroidism, goiter, the presence of ophthalmopathy or dermopathy, and a high serum thyrotropin (TSH)-receptor antibody value on at least one occasion. All the women had been treated with an antithyroid drug. When pregnant, none had a high serum TSH-receptor antibody value or was taking an antithyroid drug or thyroxine. Serum TSH, free thyroxine (T₄), and free triiodothyronine (T₃) were measured in all the women between 19 and 34 weeks of gestation.

Results The mean gestational age of the women with a history of Graves' hyperthyroidism was 27 weeks (range, 19 to 33), as was that of the normal women (range, 22 to 34). The mean serum TSH, free T₄, and free T₃ concentrations were similar in both groups of women (Table).

	Serum TSH (mU/L)	Serum Free T ₄ (ng/dl)	Serum Free T ₃ (ng/dl)
Women with a history of Graves' hyperthyroidism (n=34)	1.1	0.96	0.26
Normal women (n=102)	1.6	1.02	0.28

To convert serum free T₄ and free T₃ values to pmol/L, multiply by 12.9 and 15.4, respectively.

There were no differences in the values between 20 and 34 weeks in either group.

Conclusion Women who had hyperthyroidism caused by Graves' disease and are in remission after antithyroid drug therapy have normal thyroid function during pregnancy.

COMMENTARY

These results may not seem surprising, if the women were indeed in complete remission (e.g., were producing no TSH-receptor antibodies at all). While that seems likely, more information about the women could have been provided. How far in the past was the episode of Graves' hyperthyroidism, for how long were they treated, and what was the interval between cessation of treatment and the pregnancy? Was their thyroid function known to be normal before the pregnancy? Serum TSH-receptor antibodies were apparently measured only once. When is not stated precisely, but it was probably at the same time as serum TSH and thyroid hormones were measured, and the latter measurements were done only once.

The lack of this information does not negate the main point—women with a history of Graves' hyperthyroidism who are in remission have normal thy-

roid function in mid to late pregnancy, and therefore there is no risk of fetal or neonatal hyperthyroidism.

Did these women have normal thyroid function early in pregnancy as well? It is between 8 and 14 weeks of gestation that thyroid function in pregnant women varies the most from normal women (1). That is when serum chorionic gonadotropin concentrations are highest, and therefore when its thyroid-stimulating activity is greatest (and serum free T₄ concentrations are sometimes slightly supranormal and serum TSH concentrations subnormal in normal pregnant women). Should a pregnant woman have mild Graves' disease, and be producing some TSH-receptor antibodies (but not enough to cause overt hyperthyroidism alone), the combination of the antibodies and chorionic gonadotropin may be sufficient to cause transient hyperthyroidism at that stage of pregnancy (2,3).

Robert D. Utiger, M.D.

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Metformin may inhibit thyrotropin secretion in patients with hypothyroidism treated with thyroxine

Vigersky RA, Filmore-Nassar A, Glass AR. Thyrotropin suppression by metformin. *J Clin Endocrinol Metab* 2006;91:225-7.

SUMMARY

Background Several drugs decrease the effect of orally administered thyroxine (T_4), by decreasing its absorption or increasing its clearance. This paper describes four patients taking T_4 in whom co-administration of metformin resulted in a decrease in serum thyrotropin (TSH) concentrations, but no change in serum T_4 concentrations.

Case Reports The index patient (Patient 1) was a 58-year-old man with hypothyroidism after radioiodine therapy for hyperthyroidism who had been treated with 150 μ g of T_4 daily for four years. He was found to have nonalcoholic steatohepatitis, and was treated with 1500 mg of metformin daily. Eight months later, his serum TSH concentration was low (Table). Metformin was stopped. Two months later his serum TSH was normal. Metformin was resumed, and his serum TSH was low again. The drug was stopped again, and rosiglitazone was given, after which his serum TSH increased to 0.93 mU/L. There was no change in serum free T_4 concentration at any time.

Table. Serum TSH and Free T_4 Concentrations during Metformin Therapy in Patient 1.

Time	Metformin (mg/day)	Serum TSH (mU/L)	Serum Free T_4 (ng/dl)
Base line	0	1.6	1.2
8 months	1500	0.11	1.0
10 months	0	1.4	1.0
22 months	1500	0.11	1.1
24 months	0	0.93	1.1

To convert serum free T_4 values to pmol/L, multiply by 12.9. Normal range: serum TSH, 0.43 to 4.7 mU/L; free T_4 , 0.8 to 2.4 ng/dl (10 to 30 pmol/L).

Patient 2 was a 67-year-old woman with diabetes treated with insulin for 14 years and hypothyroidism caused by Hashimoto's thyroiditis treated with 224 μ g of T_4 daily for 5 years. Her serum TSH was 0.64 mU/L before and 0.31

mU/L after she had taken metformin, 500 mg daily, for two months, and it was 0.17 mU/L after the metformin dose was raised to 1000 mg daily. The T_4 dose was reduced to 200 μ g daily, after which her serum TSH was 0.21 mU/L (time interval not stated). Her serum free T_4 concentrations on the last two occasions were 2.3 ng/dl (30 pmol/L) and 1.4 ng/dl (19 pmol/L), respectively.

Patient 3 was a 66-year-old man with diabetes treated with glipizide for five years and hypothyroidism after thyroidectomy for multinodular goiter treated with 125 μ g of T_4 daily for four years. His serum TSH was 1.3 mU/L before and 0.36 mU/L after he had taken metformin, 1000 mg daily, for an unstated interval. The T_4 dose then was reduced to 125 μ g six days each week. After taking metformin for a total of six months, his serum TSH was 0.14 mU/L. Serum free T_4 concentrations on the last two occasions were 1.6 ng/dl (21 pmol/L) and 1.1 ng/dl (14 pmol/L), respectively.

Patient 4 was a 75-year-old woman with diabetes treated with insulin for five years and hypothyroidism after thyroidectomy for thyroid carcinoma treated with 175 μ g of T_4 daily for 50 years. Her serum TSH was 1.9 mU/L before and 0.39 mU/L after treatment with metformin, 500 mg daily, for three months, and it was 1.2 mU/L four months after metformin was discontinued. Serum free T_4 concentrations on the last two occasions were 2.8 ng/dl (36 pmol/L) and 1.9 ng/dl (25 pmol/L), respectively.

No patient had any clinical manifestations of thyroid dysfunction while taking metformin. Addition of metformin to serum in vitro did not alter the measured serum TSH value.

Conclusion Metformin reduced serum TSH concentrations slightly in patients with hypothyroidism taking adequate replacement doses of T_4 .

COMMENTARY

Does metformin indeed inhibit TSH secretion in patients with hypothyroidism who are taking T_4 ? Perhaps, but the data could be more compelling. Serum free T_4 was not measured before metformin therapy was started, and the patients were studied at different times while taking different doses of metformin. The decreases in serum TSH concentrations were small, but they occurred in the absence of high serum free T_4 concentrations, and in Patients 2 and 3, serum TSH concentrations remained low despite a reduction in T_4 dose and a fall

in serum free T_4 concentrations.

How might a drug reduce TSH secretion in patients with hypothyroidism treated with T_4 , in whom T_4 input is constant? It could increase the absorption of T_4 , decrease the production of thyroxine-binding globulin or transthyretin, or slow T_4 clearance; these actions would tend to raise serum free T_4 concentrations. It could inhibit TSH secretion by a dopamine-like action, stimulating cellular T_4 or T_3 transport, activating nuclear T_3 receptors, or potentiating the action of T_3 -nuclear T_3 receptor complexes. These actions could occur in the absence of any change in serum free T_4

concentrations, and the thyromimetic actions could occur not only in the hypothalamus or pituitary, but in many other tissues as well. Gauged by the small decrease in TSH secretion, however, it is unlikely there would be any clinical manifestations of hyperthyroidism.

These are very preliminary observations, but so many people are taking metformin, not to mention T_4 , that more information about this possible effect of metformin should be forthcoming soon.

Robert D. Utiger, M.D.

Serum thyrotropin is positively associated with higher body-mass index in normal subjects

Nyrnes A, Jorde R, Sundsfjord J. Serum TSH is positively associated with BMI. *Int J Obes (Lond)* 2006;30:100-5.

SUMMARY

Background Pituitary–thyroid function is one of many determinants of body weight, and some change in weight is common in patients with hyperthyroidism or hypothyroidism. In several studies of subjects with normal pituitary–thyroid function, serum thyrotropin (TSH) concentrations were positively related to body weight, and, less often, serum free thyroxine (T₄) concentrations were negatively related. In this cross-sectional and longitudinal study, the relationship between serum TSH and body-mass index (BMI) was determined in a large population-based cohort.

Methods Weight, height, and serum TSH were measured in 6164 subjects (3351 women, 2813 men; age range, 29 to 89 years) living in Tromsø, Norway, in 2001. These subjects represented 59 percent of those invited to participate in the study; the others declined participation or were excluded if they had taken or were taking thyroid hormone, there was no information about thyroid therapy in their record, or serum TSH was not measured. Among these subjects, 2672 had the same measurements in 1994-1995. For the analyses, only those subjects whose serum TSH concentrations were within the 2.5- to 97.5-percentile range were included, subdivided by smoking status. Approximately 25 percent were smokers, defined as those who smoked daily.

Results There was a gradual increase in serum TSH concentrations with age in both women and men, smokers and nonsmokers, in the 2001 cohort. For example, among nonsmokers, the mean serum TSH concentration was 1.6 mU/L in women aged 30 to 39 years, and it was 2.3 mU/L in those aged >69 years; the respective values in men were 1.6 and 2.3 mU/L. There was less increase with age in the smokers.

There was a gradual increase in BMI with increasing quartile of serum TSH in both women and men. Among the

nonsmokers, the differences between the lowest and highest quartiles were 1.4 kg/m² in the women and 0.4 kg/m² in the men (Table); after age-adjustment, only the difference in women was statistically significant (P for trend, <0.01). Considering serum TSH as a continuous variable and age as a covariable, serum TSH concentrations were positively associated with BMI in both women and men who were nonsmokers (P<0.01 and P<0.05, respectively). In the smokers, BMI was not associated with either quartile of serum TSH or serum TSH as a continuous variable.

Table. BMI in Relation to Quartiles of Serum TSH in Women and Men According to Smoking Status.

Serum TSH**	BMI (kg/m ²)			
	Women*		Men*	
	Nonsmokers	Smokers	Nonsmokers	Smokers
Quartile 1	26.4	24.8	26.9	25.9
Quartile 2	26.7	24.9	27.1	26.2
Quartile 3	26.7	25.4	27.2	26.3
Quartile 4	27.8	24.8	27.3	26.2

*The mean age of the subjects in these groups ranged from 52 to 64 years.
 **The quartile 1 serum TSH values were 0.5 to 1.1 mU/L in the women and 0.6 to 1.2 mU/L in the men, and the quartile 4 values were 2.2 to 4.6 mU/L in the women and 2.2 to 4.7 mU/L in the men.

Among the 2672 subjects in whom serum TSH was measured in 1994-1995 and 2001, there were 1725 (912 women, 813 men) who had normal serum TSH values at both times and in whom smoking status had not changed. Considering the women and men who were nonsmokers together, there was no association between the increase in BMI and the quartile of increase in serum TSH between 1994-1995 and 2001. When analyzed as a continuous variable the increase in BMI was positively associated with the increase in serum TSH (P<0.05), but not in women or men separately.

Conclusion In women and men who do not smoke, serum TSH concentrations are positively associated with BMI, and an increase in BMI with time is associated with an increase in serum TSH concentration.

COMMENTARY

Are variations in serum TSH or free T₄ concentrations within the normal range associated with BMI, or, in simple terms, body weight? Yes, for serum TSH concentrations among nonsmokers, according to Nyrnes et al. No, not for serum TSH or free T₄ concentrations among patients with thyroid disease but normal thyroid function, according to Manji et al. Yes, in several other studies. For example, serum TSH concentrations

were positively and serum free T₄ concentrations negatively associated with BMI among 4082 people in Denmark (1). Among 87 obese women (BMI ≥30 kg/m²), serum TSH concentrations were positively associated with increasing BMI, but there was no relationship between serum free T₄ concentrations and BMI (2). And mean 24-hour serum TSH concentrations (measured at 10-minute intervals) were higher in 11 obese women than in 11 normal-weight women (1.9 vs. 1.1 mU/L), and decreased (to 1.5 mU/L)

after they had lost 13.5 kg; serum free T₄ concentrations were similar in the two groups, and did not change after weight loss in the obese women (3).

Accepting that serum TSH concentrations and BMI are associated, although that is hardly proven, which comes first—the increase in TSH secretion or the increase in weight? If the former, it is presumably caused by a small fall in thyroid secretion. The result would be that might be called sub-subclinical hypothyroidism (high normal but not high serum

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Serum thyrotropin is not associated with body-mass index in euthyroid patients with thyroid disorders

Manji N, Boelaert K, Sheppard MC, Holder RL, Gough SC, Franklyn JA. Lack of association between serum TSH or free T₄ and body mass index in euthyroid subjects. *Clin Endocrinol (Oxf)* 2006;64:125-8.

SUMMARY

Background Thyroid function within the normal range may be a determinant of body weight, so that people who are heavier have higher serum thyrotropin (TSH) and lower serum free thyroxine (T₄) concentrations. In this cross-sectional study, the relationships between serum TSH and free T₄ concentrations and body-mass index (BMI) were determined in euthyroid patients with thyroid disorders.

Methods The study subjects were 401 patients (361 women, 40 men; mean age, 48 years), of whom 330 were white and 71 of other race/ethnicity, seen at a thyroid clinic in the United Kingdom. All had been referred to the clinic for evaluation of a thyroid nodule or goiter. History was obtained, and weight, height and serum TSH (normal range, 0.4 to 5.5 mU/L), free T₄, and antithyroid peroxidase antibodies were measured. All the patients underwent fine-needle aspiration biopsy; 27 (7 percent) proved to have thyroid carcinoma. Patients with past or present overt or subclinical thyroid dysfunction were excluded.

Results There was no correlation between BMI and serum TSH concentration ($r = 0.03$, $P = 0.62$) or serum free T₄ concentration ($r = 0.02$, $P = 0.74$) in the 401 patients, or in the women or men separately. The median BMI values were similar in subgroups of the patients formed according to tertiles of serum TSH (Table) or serum free T₄.

Table. Median BMI in Relation to Tertile of Serum TSH in 401 Euthyroid Patients.

Tertile of serum TSH	BMI (kg/m ²)
Lower (0.4-0.9 mU/L)	26.5
Middle (1.0-1.9 mU/L)	26.2
Upper (2.0-5.5 mU/L)	26.3

The median serum TSH and free T₄ concentrations also were similar in the patients who had a BMI ≥ 30 kg/m² (obese) and those with a BMI < 30 kg/m² (nonobese). There was no correlation between either serum TSH or free T₄ and BMI in the obese group.

Thirty-five of the 267 patients (13 percent) in whom serum antithyroid peroxidase antibodies were measured had a high serum titer of the antibodies. The median BMI values in the patients who had high titers and those who did not were 26.2 and 25.3 kg/m² ($P = 0.28$), respectively; and their median serum TSH concentrations were 1.9 and 1.2 mU/L ($P = 0.02$), respectively. Exclusion of non-whites, the 27 patients with thyroid carcinoma, or the 15 patients with diabetes mellitus did not alter the results.

Conclusion Serum TSH and free T₄ concentrations are not associated with BMI in euthyroid patients with thyroid nodules or goiter.

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TSH concentrations), and the consequence might be a decrease in energy expenditure and weight gain. The question then becomes, what is the cause of the fall in thyroid secretion?

If the increase in body weight comes first, what signal from increasing weight, presumably meaning increasing fat stores, increases TSH secretion? One possible signal is leptin. Its production increases with fat mass, and it stimulates TSH secretion slightly. But then why aren't serum free T₄ concentrations a little higher, rather than being (at least in some studies) negatively associated with BMI? Could it be that weight gain also induces mild thyroid resistance to TSH?

Untangling the relationships between TSH and thyroid secretion and

action and BMI should increase understanding of the hormonal regulation of energy intake and expenditure,

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Genetic deficiency of type 3 iodothyronine deiodinase in mice results in fetal and neonatal hyperthyroidism followed by central hypothyroidism

Hernandez A, Martinez ME, Fiering S, Galton VA, St Germain D. Type 3 deiodinase is critical for the maturation and function of the thyroid axis. *J Clin Invest* 2006;116:476-84.

SUMMARY

Background Normal growth and development are dependent on the availability of adequate amounts of thyroxine (T₄) and triiodothyronine (T₃). Their availability is dependent on normal pituitary and thyroid function, and on the activity of the two deiodinases (types 1 and 2) that catalyze conversion of T₄ to the more active T₃ and the deiodinase (type 3) that catalyzes conversion of T₃ and T₄, respectively, to 3,3'-diiodothyronine and reverse T₃, which are inactive. Type 3 deiodinase is present in many fetal tissues, including the brain, the placenta, and pregnant uterus, whereas it is found primarily in the brain and skin in older animals. In this study, the effects of deletion of the gene for type 3 deiodinase (*Diol3*) on growth and development; serum T₄, T₃, and thyrotropin (TSH) concentrations; and T₃ action in mice were determined.

Methods and Results The studies were done in homozygous (D3KO) mice carrying a *Diol3* gene that had been mutated so that the gene product was inactive. No type 3 deiodinase activity was detected in fetal D3KO mice or the brain, ovaries, or pregnant uterus of adult D3KO mice, and it was barely detectable in the placenta of pregnant heterozygous mice, whereas it was readily detected in these tissues in wild-type (WT) mice. Mating of heterozygous female and male mice resulted in fewer homozygous pups (17 percent, vs. 25 percent expected). Both male and female D3KO mice were less fertile than expected, and their growth was impaired.

In the WT mice, serum T₃ and T₄ concentrations were low at birth, reached a peak on the 15th postnatal day, and then declined. Their serum TSH concentrations on postnatal days 21, 90, and 240 to 390 days were approximately 200 ng/ml. As compared with WT mice, serum T₃ concentrations in the D3KO mice were slightly higher on embryonic day 19 and at birth, and considerably higher (325 percent)

on postnatal day 5, after which they declined, and were lower than in WT mice on postnatal day 15 and thereafter (Table). Their serum T₄ concentrations were very low initially, and never exceeded 50 percent of the concentrations in WT mice. Serum TSH concentrations were also very low initially, and later were only slightly higher than in WT mice.

Postnatal Day	Serum T ₃	Serum T ₄	Serum TSH
5	325%	<10%	<15%
10	125%	<10%	<25%
15	80%	<10%	<35%
21	50%	<5%	100%
90	80%	35%	160%
240-390	60%	50%	130%

*Extrapolated from Figure 4, Figure 6, and the text of the paper. Three to 33 mice per group.

The rate of clearance of radiolabeled T₃ from the plasma of 2-day-old D3KO mice was 20 percent of that of WT mice. T₃ binding to serum was similar in the two groups.

On postnatal days 1 to 3, the T₃ concentration in the brain of the D3KO mice was almost 3 times higher than in WT mice, and the brain messenger RNA (mRNA) content of two T₃-stimulated genes, *RC3* and *Hairless*, was increased. On postnatal day 5, the brain content of type 2 deiodinase was slightly higher in D3KO mice than in WT mice, and it was approximately 5 times higher on postnatal days 10, 15, and 21. In adult mice, the hypothalamic content of T₃ was lower, the hypothalamic content of thyrotropin-releasing hormone (TRH) mRNA was higher, and hepatic type 1 deiodinase mRNA and activity were lower in the D3KO mice.

Conclusion Deletion of the *Diol3* gene results in slowing of T₃ clearance, high serum T₃ concentrations, and increased T₃ action in tissue in fetal and neonatal mice, and central hypothyroidism in older mice.

COMMENTARY

Did the D3KO mice indeed have fetal and neonatal hyperthyroidism and central hypothyroidism later? The evidence for the former is substantial: high serum T₃ and tissue (brain) T₃ concentrations, low serum TSH concentrations, increased expression of several T₃-stimulated genes in the brain, and poor prenatal and neonatal growth. The excess T₃ in these mice was presumably a result of decreased deiodination of both maternal and fetal T₃, resulting from decreased

type 3 deiodinase deficiency in both the placenta and fetal–neonatal tissue. The excess T₃ inhibited TSH secretion, and therefore thyroidal secretion of T₄ must have been low.

The evidence that the older mice had central hypothyroidism is also substantial. They had low serum T₃ and T₄ concentrations, with only minimal elevations in serum TSH concentrations (and the TSH probably had decreased biologic activity), and had several consequences of hypothyroidism, including decreased type 1 deiodinase activity in the liver,

increased type 2 deiodinase activity in the brain, and increased content of TRH mRNA in the hypothalamus.

No humans with a loss-of-function mutation in type 3 deiodinase have been described, but a somewhat similar pattern of fetal and neonatal hyperthyroidism and subsequent central hypothyroidism has been described in infants of mothers with Graves' disease.

Robert D. Utiger, M.D.

Special Article

The American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2006;16:109-41. (<http://thyroid.org/professionals/publications/documents/Guidelinesthy2006.pdf>, accessed March 16, 2006)

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Abraham P, Avenell A, Park CM, et al. A systematic review of drug therapy for Graves' hyperthyroidism. *Eur J Endocrinol* 2005;153:489-98.

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Corrections

The antitumor drug imatinib increases the requirement for thyroxine in patients with hypothyroidism (November 2005;17:51). The page numbers for the citation for the original article (De Groot, JW, Zonnenberg BA, Plukker JT, et al. *Clin Pharmacol Ther* 2005;78:4334-8) are wrong. The correct page numbers are 433-8.

An increase in serum thyroglobulin after thyrotropin administration indicates persistent tumor in patients with thyroid carcinoma (November 2005;17:56). The last sentence of the second paragraph of the Methods section of the Summary should read "The basal serum Tg values in these 11 patients were ≤ 0.5 ng/ml in 7 and 0.6 to 1.0 ng/ml in 4." The ≤ 0.5 ng/ml value was mistakenly given as ≤ 5 ng/ml.

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