

# CLINICAL THYROIDOLOGY

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# CLINICAL THYROIDOLOGY

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## Graves' Disease - An Often Ill-Used Term

It is commonplace to refer to patients who have hyperthyroidism as having Graves' disease, as in "I was called today about a patient with Graves disease", or, worse, just Graves, as in "I saw a patient with Graves today" or "Can I give radioiodine to this patient with Graves?" This shorthand, jargon is a better term, ignores the fact that the patient's problems nearly always concern hyperthyroidism, whatever its cause, and that the treatment is for hyperthyroidism, not Graves' disease.

Graves' disease is a constellation of five clinical problems. They are—in descending frequency—hyperthyroidism, goiter, ophthalmopathy, localized myxedema, and thyroid acropachy. The problems with the glib use of the term Graves' are that the most common manifestations of Graves' disease, which are hyperthyroidism and goiter, are not at all specific for Graves' disease, and there is no treatment for Graves' disease.

So why the continued casual, and inappropriate, use of the term Graves' disease when hyperthyroidism is what is meant?

One is that Graves' disease is widely thought to be the most common cause of spontaneously occurring hyperthyroidism, and it is the only cause for which there is a short eponym. (Yes, there is Plummer's disease and Basedow's disease, but does anyone ever say "I saw a patient with Plummer's, or Basedow's, today"?) This makes it very easy to equate hyperthyroidism with Graves' disease, with little thought about the distinction between the two, specifically the presence of findings that suggest that the patient with hyperthyroidism indeed has Graves' disease, or the presence of findings that indicate that the cause is something else. (Whether Graves' disease is the most common cause of spontaneously occurring hyperthyroidism is not certain; there are no studies in which the causes of hyperthyroidism in patients presenting to primary care physicians were carefully determined.)

A second is that the cause of hyperthyroidism is usually determined primarily on the basis of the patient's history and clinical findings, and appropriately so. In this context Graves' disease is the default. If there are no fairly obvious findings indicating another cause, for example a long history of asymmetric goiter or thyroid pain and tenderness, the patient is assumed to have Graves' disease.

Last, but probably most important of all, is the penchant among physicians for jargon, preferably, of course, very terse jargon. It is easier to say Graves' disease, or just plain Graves', than hyperthyroidism caused by Graves' disease or even Graves' hyperthyroidism. Everyone should know what is meant, meaning everyone should know that the patient has hyperthyroidism, whatever the cause. But it is wrong.

Hyperthyroidism and Graves' disease are not synonymous, and they should not be spoken of as if they are.

Robert D. Utiger, M.D.

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*Clinical Thyroidology* is available on the ATA web site ([www.thyroid.org](http://www.thyroid.org))

## The prevalence but not the incidence of hyperthyroidism and hypothyroidism increased during the 1990s in a community in Scotland

Flynn RW, MacDonald TM, Morris AD, Jung RT, Leese GP. The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. *J Clin Endocrinol Metab* 2004;89:3879-84.

### SUMMARY

**Background** Data concerning the frequency of hyperthyroidism and hypothyroidism are rare. The goal of this study was to determine their prevalence and incidence in a large community during a period of several years.

**Methods** The study group consisted of all subjects living in Tayside, Scotland, who were registered continuously with a general practitioner between January 1, 1993, and April 30, 1997. Those with thyroid disease were identified from a master patient index; the Tayside thyroid register, which automatically follows patients treated with thyroid hormone; a database containing patient-specific prescription data; a database containing radioiodine treatment data for the region; and Scottish mortality records. Patients with thyroid cancer and those treated with thyroid hormone for goiter were excluded.

Subjects were considered to have hyperthyroidism if they had been treated with an antithyroid drug or radioiodine, or if they had low serum thyrotropin (TSH) values before thyroid surgery. Prevalent (existing) cases were those with hyperthyroidism from January through June 1993, and incident (new) cases were those newly treated from July 1993 through April 1997. Subjects were considered to have hypothyroidism if they had received continuous thyroid hormone therapy, including during the 6 months before either the end of the study or their death. Prevalent cases of hypothyroidism were those treated from January through June 1993, and incident cases were those newly treated from July 1993 through October 1996 (patients with hypothyroidism after treatment for other thyroid disorders were excluded).

Review of the general-practice records of 87 patients with hyperthyroidism and 363 patients with hypothyroidism revealed 98 and 96 percent agreement, respectively, with the electronic databases.

**Results** There were 1910 prevalent cases in 1993 and 620 incident cases of hyperthyroidism from 1993 to 1997. During this interval, the midyear point prevalence increased significantly, from 0.51 to 0.63 percent ( $P < 0.001$ ) (Table). Among the 620 incident cases, 526 (85 percent) were females and 94 (15 percent) were males. The overall (1993–1997) incidence rate was 0.46 per 1000 person-years. No cases were  $< 9$  years old. The overall incidence rates (by decade of age) among adult women ranged from 0.78 to 1.29 per 1000 person-years, and those for men ranged from 0.06 to 0.45 per 1000 person-years.

	1993	1994	1995	1996
Population	350,136	349,884	349,626	349,369
<b>Hyperthyroidism</b>				
Prevalent cases	1791 (0.51%)	1933 (0.55%)	2040 (0.58%)	2188 (0.63%)
Incident cases (previous 12 months)		188	157	207
Incidence rate (per 1000 person-years)		0.54	0.45	0.59
<b>Hypothyroidism</b>				
Prevalent cases	7627 (2.18%)	8466 (2.42%)	9471 (2.71%)	10,408 (2.98%)
Incident cases (previous 12 months)		1114	1286	1233
Incidence rate (per 1000 person-years)		3.18	3.68	3.53

For hypothyroidism, there were 5436 prevalent cases, and 3469 incident cases. The midyear point prevalence increased from 2.18 to 2.98 percent ( $P < 0.001$ ). The incident cases included 2969 females (86 percent) and 500 males (14 percent). The overall (1993–1997) incidence rate was 2.97 per 1000 person-years. Twenty cases were  $< 9$  years old. Among adult women the overall incidence rates ranged from 1.83 to 9.72 per 1000 person-years, and for men they were 0.24 to 4.85 per 1000 person-years.

**Conclusion** Among subjects living in the Tayside region of Scotland, the prevalence, but not the incidence, of hyperthyroidism and hypothyroidism increased during the 1990s.

### COMMENTARY

The main criterion for diagnosis in this study was that some antithyroid or thyroid hormone therapy was given, although this was not stated explicitly. Thus, the lack of an increase in new (incident) cases of hyperthyroidism or hypothyroidism from 1993 to 1997 indicates there was no change in detec-

tion of thyroid dysfunction of sufficient severity to warrant therapy. This does not seem surprising given the short duration of the study. Alternatively, an increase in incidence could have been counterbalanced by a decrease in ascertainment and treatment, but that seems very unlikely. The increase in prevalence of both hyperthyroidism and hypothyroidism attests to continued effective antithyroid

and thyroid therapy and no preferential mortality among the treated subjects.

Robert D. Utiger, M.D.

## Male sex and increasing age are the major risk factors for atrial fibrillation in patients with hyperthyroidism

Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. *Arch Intern Med* 2004;164:1675-8.

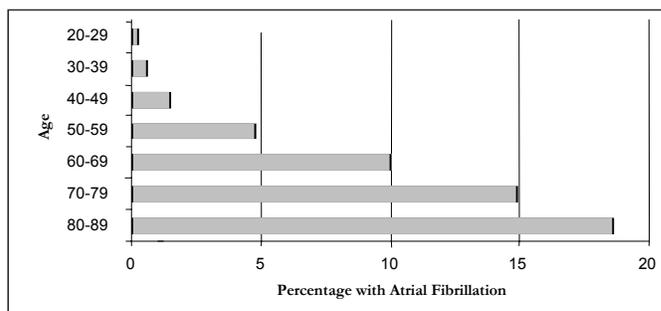
### SUMMARY

**Background** Atrial fibrillation is a well-recognized manifestation of hyperthyroidism, but its reported prevalence has varied widely, and the risk factors for it are not well understood. This study was done to determine the factors associated with atrial fibrillation in a large group of patients with hyperthyroidism.

**Methods** All patients with a hospital discharge diagnosis of hyperthyroidism from January 1977 through December, 1999, and all patients with an outpatient diagnosis of hyperthyroidism from January, 1995, through December 1999 were identified in the Danish National Registry of Patients. All patients with a diagnosis of atrial fibrillation or flutter (coded together during part of the study period) during the same intervals were similarly identified. Most patients had an electrocardiogram at admission, and those with atrial fibrillation were usually screened for hyperthyroidism. Data on hypertension, ischemic heart disease, valvular heart disease, heart failure, and diabetes mellitus before or at the time of diagnosis of hyperthyroidism also were obtained from the registry. Patients younger than 20 years or older than 89 years and patients with onset of atrial fibrillation more than 30 days before or after the diagnosis of hyperthyroidism were excluded.

**Results** There were 40,628 patients with hyperthyroidism (34,513 women [85 percent], 6115 men [15 percent]); 48 percent were aged 20 to 59 years, and 52 percent were aged 60 to 89 years. Five percent had hypertension, 7 percent had ischemic heart disease, 1 percent had valvular heart disease, 4 percent had heart failure, and 4 percent had diabetes.

Among the patients with hyperthyroidism, 3362 (8 percent) had atrial fibrillation (women, 2621 of 34,513 [8 percent]; men, 741 of 6115 [12 percent]). The frequency of atrial fibrillation increased markedly with age, ranging from 0.3 percent among the patients aged 20 to 29 years to 19 percent of those aged 80 to 89 years (Figure).



The risk factors for atrial fibrillation are shown in the Table.

	Adjusted Odds Ratio*
Men (women as reference group)	1.7 (1.6-1.9)
Age at diagnosis of hyperthyroidism (per 10-year increment)	1.7 (1.7-1.8)
Comorbidity (no comorbidity as reference group)	
Hypertension	1.1 (0.9-1.3)
Ischemic heart disease	1.8 (1.6-2.0)
Valvular heart disease	2.6 (1.9-3.4)
Heart failure	3.9 (3.5-4.4)
Diabetes mellitus	1.0 (0.8-1.2)

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

**Conclusion** Among patients with hyperthyroidism, atrial fibrillation is more common in men than in women, and its frequency increases markedly with age.

### COMMENTARY

Atrial fibrillation, like cardiac failure, is not an adequate diagnosis, and it should prompt a search for the cause. In a review of patients attending a cardiology clinic with a diagnosis of “idiopathic” (or “lone”) atrial fibrillation, 13 percent had overt or subclinical hyperthyroidism (1). While Frost et al. found that ischemic and valvular heart disease and congestive heart failure all increased the risk of atrial fibrillation, many patients had none of these abnormalities; they had idiopathic hyperthyroid atrial fibrillation. Thus, thyroid function testing should be routine in all patients with atrial fibrillation, because the clinical features of hyperthyroidism in the elderly may be subtle, and helpful signs, such as goiter

and exophthalmos, may be absent. Interpretation of the test results, particularly low serum thyrotropin values, may be complicated because the values may be low as a result of nonthyroidal illness.

There are two outstanding issues in relation to atrial fibrillation in patients with hyperthyroidism. They are the risk of systemic embolization and the optimal time to perform cardioversion. The risk of systemic embolization in hyperthyroid patients with atrial fibrillation may be as great as in patients with rheumatic mitral valve disease, and anticoagulation with warfarin is indicated. Given that hyperthyroid cardiomyopathy is not reversible for at least six weeks after restoration of normal thyroid secretion (2), there should be a similar delay after normalization of serum TSH before

direct-current cardioversion is attempted.

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## Bone density is low and increases after treatment in women with hyperthyroidism

Karga H, Papapetrou PD, Korakovouni A, Papandroulaki F, Polymeris A, Pampouras G. Bone mineral density in hyperthyroidism. *Clin Endocrinol (Oxf)* 2004;61:466-72.

### SUMMARY

**Background** Hyperthyroidism is a well-known cause of low bone density, but the extent to which it is reversed by antithyroid therapy is not well known. In this cross-sectional study bone density was measured in a large group of women with hyperthyroidism at the time of diagnosis or up to three decades later.

**Methods** The study subjects were 164 white women with present or past overt hyperthyroidism and 79 normal women. Women with a body mass index <19 or >25 kg/m<sup>2</sup> of body-surface area, a history of major medical illness or overt bone disease, or treatment for osteopenia or osteoporosis (excepting those taking calcium or vitamin D supplements) were excluded. Among the women with hyperthyroidism, 143 (87 percent) had Graves' disease and 21 (13 percent) had a nodular goiter. Treatment consisted of an antithyroid drug alone in 107 women (65 percent), radioiodine in 49 women (30 percent), and surgery in 8 women (5 percent); 48 women (29 percent) had hypothyroidism and were receiving thyroxine. The women were divided into three groups according to the time between diagnosis and study. Bone mineral density of the femoral neck and lumbar spine (L2–L4) was measured by dual-photon absorptiometry, and the results expressed as Z scores (deviation from values in women of similar age) and T scores (deviation from values in young women).

**Results** The women studied at the time of diagnosis of hyperthyroidism or soon thereafter had a lower femoral-neck than lumbar-spine bone density Z score (Table 1). As compared with the women studied at 0 to 0.09 years, the women studied at 0 to 3 years had a higher femoral-neck Z score and a lower lumbar-spine Z score. The values were nearly 0 at both sites in the women studied 3.1 to 31 years after diagnosis.

Table 1. Bone Mineral Density (BMD) of the Femoral Neck and Lumbar Spine in Women with Hyperthyroidism at Diagnosis or at Varying Intervals Thereafter and Control Women.

Time Interval (yr)*	Mean Age (yr)	Mean Femoral Neck BMD (Z score)	Mean Lumbar Spine BMD (Z-score)
0-0.09 (n=19)	37	-0.42	-0.11
0-3 (n=68)	44	-0.30	-0.29
3.1-31 (n=96)	57	-0.04	-0.07

\*Time interval between diagnosis of hyperthyroidism and bone densitometry.

When considered in relation to age at the time of diagnosis of hyperthyroidism, the mean femoral neck Z score 0 to 3 years later was -0.26 in 25 women aged 13 to 30 years at diagnosis, and at 3.1 to 31 years it was 0.40. The respective values in 75 women aged 31 to 50 years at diagnosis were -0.20 and -0.10, and those in 41 women aged 51 to 70 years at diagnosis were -0.51 and -0.14. The mean lumbar-spine Z scores were similar, with the younger women gaining more bone density with time.

The proportions of women with hyperthyroidism in the past and normal women who had osteoporosis or osteopenia were similar (Table 2).

Table 2. Proportions of Women with Hyperthyroidism in the Past (>3 Years) and Normal Women with Osteoporosis (T Score, -2.5 or Lower) and Osteopenia (T Score, -1.0 to -2.4).

	Osteoporosis	Osteopenia	Normal
<b>Femoral Neck</b>			
Hyperthyroid/normal women (age ≥51 yr)	42%/29%	40%/50%	18%/21%
Hyperthyroid/normal women (age ≤50 yr)	0%/0%	23%/31%	77%/69%
<b>Lumbar Spine</b>			
Hyperthyroid/normal women (age ≥51 yr)	41%/33%	34%/28%	25%/40%
Hyperthyroid/normal women (age ≤50 yr)	0%/3%	24%/21%	77%/76%

**Conclusion** Women of any age with hyperthyroidism may have low femoral neck and lumbar spine bone density, which increases to normal with time after treatment.

### COMMENTARY

Bone resorption is increased in women (and men) with hyperthyroidism. So is bone formation, but to a lesser extent. The result is osteopenia or osteoporosis in some patients. The changes are reversible within several years after antithyroid therapy alone, as found in this study and a meta-analysis (1).

Is there an increase in fracture risk in patients with hyperthyroidism? There were no fracture data in this study, but in

the meta-analysis (of results of five studies) (1), the risk of hip and spine fractures was slightly increased in untreated patients (relative risk, 2.0 for both) but was not increased in treated patients. There is no reason to measure bone density in patients with hyperthyroidism, but it is reassuring to know that any deficit is repaired.

Robert D. Utiger, M.D.

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1. Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk—a meta-analysis. *Thyroid* 2003;13:585-93.

## Transient recurrences of hyperthyroidism may occur after antithyroid drug therapy in patients with Graves' hyperthyroidism

Kubota S, Tamai H, Ohye H, Fukata S, Kuma K, Miyauchi A. Transient hyperthyroidism after withdrawal of antithyroid drugs in patients with Graves' disease. *Endocr J* 2004;51:213-7.

### SUMMARY

**Background** Patients with hyperthyroidism caused by Graves' disease are often treated with an antithyroid drug for a prolonged period. Subsequently, many patients have recurrent hyperthyroidism, and drug treatment is resumed or another treatment is given. This retrospective study describes the occurrence of recurrent hyperthyroidism that subsided spontaneously in patients previously treated for Graves' hyperthyroidism.

**Methods** From 1998 to 2002, 22 patients with Graves' hyperthyroidism who had mild transient hyperthyroidism after completion of a course of antithyroid drug therapy were followed without resumption of therapy. Twenty were women and two were men; their mean ( $\pm$ SD) age was  $34\pm 13$  years. Twenty had been treated with methimazole and two with propylthiouracil; the mean duration of therapy was 39 months (range, 6 to 144). All had normal thyroid function and normal serum tests for thyrotropin (TSH)-binding inhibitory immunoglobulins (TBII), measured by receptor assay, when therapy was stopped. Patients who had "unbearable" symptoms of hyperthyroidism or were elderly, neither defined, at the time of recurrence were excluded (number not given).

**Results** The interval from cessation of antithyroid drug therapy to recurrent hyperthyroidism was  $6\pm 4$  months

(range, 1 to 12); it was  $\leq 6$  months in 16 patients (73 percent). At that time, their mean thyroid weight was  $33\pm 17$  g. Their serum TSH values were undetectable ( $<0.07$  mU/L). Their mean serum free thyroxine ( $T_4$ ) concentration was  $2.0\pm 0.5$  ng/dl ( $26\pm 6$  pmol/L); 9 patients (41 percent) had values within the normal range (subclinical hyperthyroidism) and 13 (59 percent) had high values (overt hyperthyroidism). Three patients (14 percent) had high and 19 patients (86 percent) had normal serum TBII values. Thyroid radioiodine uptake, measured in six patients, was  $<3$  percent in 24 hours in two patients, and ranged from 28 to 38 percent in the other four patients.

Once high, the patients' serum free  $T_4$  concentrations fluctuated little before declining, and they became euthyroid (not otherwise defined)  $6\pm 5$  months after their peak serum free  $T_4$  concentrations. None later had another recurrence of hyperthyroidism. The overall follow-up period, from cessation of antithyroid drug therapy to last observation, was  $28\pm 13$  months.

Two patients were considered to have silent thyroiditis and the other 20 to have recurrent Graves' disease.

**Conclusion** Some patients with Graves' hyperthyroidism who are treated with an antithyroid drug later have recurrent hyperthyroidism that subsides spontaneously.

### COMMENTARY

Some of these patients had Graves' hyperthyroidism that came, went away during antithyroid drug therapy, and then came back—as either subclinical hyperthyroidism or overt hyperthyroidism—and without therapy went away again. At a minimum, this occurred in seven of the patients, the three who had high serum TBII values and the four who had a normal or high thyroid radioiodine uptake, but it could have occurred in some of the others in whom thyroid radioiodine uptake was not measured (and assuming that not all patients with mild hyperthyroidism have high serum TBII values).

Therefore, documentation that many of the patients had a recurrence and then spontaneous remission of a second episode of Graves' hyperthyroidism was

less than optimal. Accepting that this sequence does occur, how common is it? The authors do not say how many patients with Graves' hyperthyroidism they treated with an antithyroid drug who either remained euthyroid for a prolonged period after therapy was stopped or had recurrent hyperthyroidism with unbearable symptoms, to use their term. They do say that they treated 1599 new patients with Graves' hyperthyroidism in 1998. Therefore, the sequence of events described in these 22 patients is likely to be rare.

If transient recurrent hyperthyroidism can occur in patients previously treated with an antithyroid drug, transient hyperthyroidism surely can occur at the onset of Graves' disease. If that is true, then there are patients with new-onset subclinical hyperthyroidism or overt

hyperthyroidism caused by Graves' disease who will have a spontaneous remission, and therefore benefit little from therapy. The problem is how to identify them.

Robert D. Utiger, M.D.

## Radioactive iodine therapy is effective and safe in children and adolescents with hyperthyroidism

Read CH Jr, Tansey MJ, Menda Y. A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. *J Clin Endocrinol Metab* 2004;89:4229-33.

### SUMMARY

**Background** Relatively few children or adolescents with hyperthyroidism are treated with radioactive iodine (I-131), because of fears of genetic damage or thyroid or other tumor formation. In this study the long-term effects of I-131 therapy in children and adolescents with hyperthyroidism were evaluated.

**Methods** Between 1953 and 1973, 116 patients <20 years old with hyperthyroidism were treated with I-131 at the University of Iowa Medical Center. In 1990–1991, 107 of the patients were located and two were known to have died. In 2001–2002, 98 of the patients were located, and five were known to have died. The seven deaths were due to cardiovascular or pulmonary diseases, seizures, toxic hepatitis, or diabetic ketoacidosis (and possibly severe hyperthyroidism in one patient). The patients and their physicians completed questionnaires about the patients' health, including questions about recurrent hyperthyroidism, hypothyroidism, and reproductive function and outcomes.

**Results** At the time of diagnosis, the 107 patients (80 females, 27 males) ranged in age from 3.6 to 19.8 years; 45 were aged 16 years or older. The mean dose of I-131 was 3 to 4 mCi (111 to 148 MBq) from 1953 to 1965; during this period many patients had persistent hyperthyroidism and were retreated within six months. The dose was gradually increased to 7 mCi (259 MBq); at this dose no patient had persistent hyperthyroidism.

These 107 patients were followed for an average of 26 years (mean age at follow-up, 40 years). One year after treatment, 34 (32 percent) had hypothyroidism. Among the 98 patients

followed for an average of 36 years (mean age at follow-up, 48 years, 96 (98 percent) had hypothyroidism. After one year, the annual rate of hypothyroidism was 3 percent. Six patients had recurrent hyperthyroidism 10 to 21 years after their original treatment, including one who had hypothyroidism and had been treated with thyroxine for 16 years.

Sixty-two females had 179 pregnancies. The outcome was: spontaneous abortion, 19; induced abortion, 5; ectopic pregnancy, 2; molar pregnancy, 1; stillbirth, 3; and live births, 152 (2 of these infants died within 12 hours of birth). Five infants (3 percent) had one or more congenital anomalies (hare lip, left heart outflow obstruction, club foot, hydrocoele, and misplaced ureter). Among the 18 females who had no pregnancies, 13 were single, 1 had an infertile spouse, and 4 were married but childless. Eighteen of the 27 males had fathered 36 pregnancies. The outcome was: spontaneous abortion, 3; and live birth, 33; no infant had a congenital anomaly. Among the 9 males who fathered no pregnancies, 5 were single, 3 had infertile spouses, and 1 was married but childless.

Two patients had a benign thyroid nodule, but none had a thyroid carcinoma. One patient had a parathyroid adenoma resected 14 years after I-131 therapy. One patient had a carcinoma of the colon and one a carcinoma of the breast. No patient had leukemia.

**Conclusion** Among children and adolescents with hyperthyroidism treated with I-131 and followed for up to 36 years, nearly all had hypothyroidism, but their reproductive capacity and outcomes were not unusual and none had thyroid carcinoma or leukemia.

### COMMENTARY

Relatively few children and adolescents with hyperthyroidism have been treated with I-131, at least in comparison with the many thousands of adults. The reason is not lack of efficacy, but fear of induction of thyroid or other tumors, reproductive dysfunction, or oocyte or sperm damage. No previous study has provided evidence for any of these effects, but the studies were small and the duration of follow-up was relatively short. These new data, based on follow-

up of nearly 100 patients for nearly 40 years, provide further evidence that I-131 therapy is safe, albeit at the cost of hypothyroidism. Indeed, hypothyroidism may protect against the carcinogenic effects of I-131 on the thyroid gland.

The authors say that I-131 was adopted as the treatment of choice for young patients with Graves' disease—of course they meant hyperthyroidism or more specifically hyperthyroidism caused by Graves' disease—at their institution in 1953. It is doubtful that it is the treatment of choice for young patients in

most places, but should it be? No. It should be considered no less for these patients than for adults, but not to the exclusion of antithyroid drug therapy or subtotal thyroidectomy.

Robert D. Utiger, M.D.

## Some patients with antithyroid drug–induced agranulocytosis have normal white blood cell counts

Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: special reference to normal white blood cell count agranulocytosis. *Thyroid* 2004;14:459-62.

### SUMMARY

**Background** Agranulocytosis is the major life-threatening side effect of antithyroid drug therapy. Most patients with antithyroid drug–induced agranulocytosis have low total white blood cell (WBC) counts, but some do not. This retrospective study describes the clinical and hematologic findings in a large group of patients with agranulocytosis.

**Methods** From 1975 to 2001, 30,798 patients (23,646 women, 7152 men) with hyperthyroidism caused by Graves' disease were treated with an antithyroid drug at a clinic in Japan. WBC counts were done every two weeks during the first two months of therapy and monthly hereafter. Therapy was stopped when agranulocytosis, defined as a granulocyte count of  $<0.5 \times 10^9/L$ , was detected.

Initially, three patterns of onset of agranulocytosis were identified: symptomatic onset, in which agranulocytosis was detected when the patient had symptoms of infection; asymptomatic-to-symptomatic onset, in which agranulocytosis was detected by monitoring, therapy was stopped, and the patient became symptomatic several days later; and asymptomatic throughout. Starting in 1990, all patients with agranulocytosis were treated with granulocyte colony-stimulating factor (G-CSF). Because this therapy could prevent symptoms, patients seen thereafter were assigned only to the symptomatic-onset group or the asymptomatic group.

**Results** During the 26-year study period, 109 patients (0.35 percent) had agranulocytosis (103 women, 6 men; mean age, 40 years [range, 8 to 72]). Ninety-three of the 109 patients were among the 26,425 patients (0.4 percent) treated with

methimazole, and 16 were among the 4373 patients (0.4 percent) treated with propylthiouracil. No patient died (information supplied by the authors).

From 1975 to 1989, 71 patients had agranulocytosis, of whom 20 (28 percent) had symptomatic agranulocytosis, 17 (24 percent) had asymptomatic-to-symptomatic agranulocytosis, and 34 (48 percent) had asymptomatic agranulocytosis. From 1990 to 2001, 38 patients had agranulocytosis; 22 (58 percent) had symptomatic agranulocytosis and 16 (42 percent) had asymptomatic agranulocytosis. In total, 67 of the 109 patients (61 percent) were asymptomatic when agranulocytosis was detected.

Eighteen of the 109 patients (16 percent) had a WBC count of  $>3.0 \times 10^9/L$  at the time of diagnosis of agranulocytosis, of whom 4 (22 percent) had symptomatic agranulocytosis, 3 (17 percent) had asymptomatic-to-symptomatic agranulocytosis, and 11 (61 percent) had asymptomatic agranulocytosis. Five of these 18 patients had a WBC count of  $\geq 4.0 \times 10^9/L$  when agranulocytosis was detected. The duration of agranulocytosis in the 18 patients ranged from 1 to 13 days.

During therapy, 670 patients (2 percent) had a WBC count of  $<3.0 \times 10^9/L$  and 3347 patients (11 percent) had a WBC count of  $3.0$  to  $3.9 \times 10^9/L$  but no agranulocytosis on at least one occasion.

**Conclusions** Some patients with hyperthyroidism treated with methimazole or propylthiouracil have agranulocytosis despite having a WBC count of  $\geq 3.0 \times 10^9/L$ .

### COMMENTARY

This is the largest compilation of cases of antithyroid drug–induced agranulocytosis yet reported. As such, it offers unique insights into the problem, particularly because all the patients had WBC counts at regular intervals during therapy. Perhaps the most important finding was that the majority of patients who had agranulocytosis were asymptomatic when it was first detected, and most of them remained asymptomatic after the drug was stopped (a few, perhaps, because they received G-CSF). Would the asymptomatic patients have had symptoms or have recovered spontaneously had the drug not been continued? No one knows, nor is anyone willing to chance it, but it

seems possible that in some patients with relatively mild agranulocytosis ( $0.35$  or  $0.45 \times 10^9/L$ , for example) the cell count might rise despite continued therapy.

Does the relatively high frequency of asymptomatic agranulocytosis among the few patients with agranulocytosis overall mandate routine WBC-count or granulocyte-count monitoring, neither practice currently widespread? The authors' answer is that WBCs should be counted, but granulocytes need be counted only if the WBC count is  $<4.0 \times 10^9/L$ , because they found agranulocytosis in only 5 patients with a WBC count of  $\geq 4.0 \times 10^9/L$ . However, before any monitoring is widely adopted, several questions should be considered. Should all patients be tested, or are there high-risk

patients, as defined by age; some baseline clinical, hematologic, or biochemical characteristic; or dose of drug? What is the optimal frequency of testing and how long should it be continued? More important, what about cost and inconvenience for many patients, versus decreased morbidity in the few patients in whom agranulocytosis is detected by monitoring and who remain asymptomatic after the drug is stopped? In this study, the former group consisted of 30,748 patients, and the latter of 50 patients (0.2 percent).

Robert D. Utiger, M.D.

## Subclinical hypothyroidism may progress to overt hypothyroidism or disappear

Diez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. *J Clin Endocrinol Metab* 2004;89:4890-7.

### SUMMARY

**Background** Subclinical hypothyroidism, defined as a high serum thyrotropin (TSH) and a normal free thyroxine (T<sub>4</sub>) concentration, is common. Its consequences are not known, but it can progress to overt hypothyroidism (high serum TSH and low free T<sub>4</sub> concentrations). In this study a cohort of patients with subclinical hypothyroidism was followed to determine the risk of overt hypothyroidism.

**Methods** The study group consisted of 107 patients (93 women, 14 men; mean age, 62 years [range, 55 to 83]) with subclinical hypothyroidism. It was detected initially as an incidental finding, and confirmed by repeat study 1 to 3 months later, after which the patients were enrolled in this study. None of the patients had a history of thyroid disease. Forty-seven patients (44 percent) had one or more symptoms and signs of hypothyroidism, 9 (8 percent) had a goiter, and 81 (76 percent) had a high serum antithyroid peroxidase (TPO) antibody concentration. Seventy-five patients (70 percent) had other disorders, such as diabetes mellitus, hypertension, and ischemic heart disease.

At six-month intervals, the patients' clinical status was evaluated, and serum TSH and free T<sub>4</sub> were measured. Patients who had a serum TSH concentration  $\geq 20$  mU/L or a serum free T<sub>4</sub> concentration  $< 0.75$  ng/dl (9.7 pmol/L) during follow-up were considered to have overt hypothyroidism and were treated with T<sub>4</sub>. For comparative purposes, the patients were subdivided into three groups according to their base-line serum TSH concentration (normal range, 0.4 to 5.0) (Table). There were no differences in age, sex, body mass index, symptoms of hypothyroidism, or serum lipid values in the three subgroups.

**Results** During a mean follow-up period of 32 months (range, 6 to 72), 28 patients (26 percent) were treated with T<sub>4</sub>. The indication for treatment was a serum TSH value

$\geq 20$  mU/L in 9 patients, a serum free T<sub>4</sub> value  $< 0.75$  ng/dl (9.7 pmol/L) in 10 patients, and both changes in 9 patients. The overall incidence of overt hypothyroidism was 0.09 cases per patient-year (Table); most of the cases occurred in the first year of follow-up. During the same interval, serum TSH concentrations became normal in 40 patients (37 percent). Overt hypothyroidism was more likely to occur in patients with higher base-line serum TSH concentrations, and normalization of TSH secretion in those with lower base-line serum TSH concentrations.

	Overt Hypo- thyroidism	Incidence Rate (per patient-year)	Subclinical Hypothyroidism	Normal Serum TSH
All (n=107)	28 (26%)	0.09	39 (36%)	40 (37%)
Base-line serum TSH (mU/L)				
5.0-9.9 mU/L (n=71)	4 (6%)	0.02	30 (42%)	37 (32%)*
10.0-14.9 mU/L (n=15)	6 (40%)	0.20	7 (47%)	2 (13%)*
15.0-19.9 mU/L (n=21)	18 (86%)	0.73	2 (9%)	1 (5%)*
Serum anti-TPO antibodies				
Normal (n=26)	2 (8%)	0.02	8 (31%)	16 (61%)*
High (n=81)	26 (32%)	0.32	31 (38%)	24 (30%)*

\*P<0.01, for the distribution of patients in the overt hypothyroidism, subclinical hypothyroidism, and normal serum TSH groups at the end of follow-up.

Higher base-line serum anti-TPO antibody concentrations (Table) and lower serum free T<sub>4</sub> concentrations were associated with progression to overt hypothyroidism, but not age or sex.

**Conclusion** Among patients with subclinical hypothyroidism, progression to overt hypothyroidism is common in those who have serum TSH concentrations of 15.0 to 19.9 mU/L, whereas normalization of TSH secretion is common in those who have serum TSH concentrations of 5.0 to 9.9 mU/L.

### COMMENTARY

This is an important study, because the study patients were identified by chance, the subclinical hypothyroidism was documented to be persistent at base line, and patients with all grades of subclinical hypothyroidism were enrolled. Few would argue against treating patients with a serum TSH value  $\geq 20$  mU/L, whether symptomatic or not, but it is too bad that the elevation wasn't confirmed a few weeks later before T<sub>4</sub> treatment was

initiated. And why were patients who had a fall in serum free T<sub>4</sub>, but not a rise in serum TSH, treated? (If those 10 patients are excluded, then 18 patients [17 percent] had progression to overt hypothyroidism, though of course it could have happened later in others.)

One of the arguments for treatment of patients with subclinical hypothyroidism is that it prevents progression to overt hypothyroidism. That clearly does occur, depending on the base-line serum TSH concentration, and also the base-line

serum anti-TPO antibody concentration. Often forgotten, however, is the fact that in some patients, especially those with slightly high serum TSH concentrations (and including some patients with high serum anti-TPO antibody concentrations), subclinical hypothyroidism does not persist. This fact should certainly temper enthusiasm for treatment of all patients with this disorder.

Robert D. Utiger, M.D.

## Hypothyroidism and other pituitary hormone deficiencies occur after head injury or subarachnoid hemorrhage

Aimaretti G, Ambrosio MR, Di Somma C, Fusco A, Cannavo S, Gasperi M, Scaroni C, De Marinis L, Benvenaga S, degli Uberti EC, Lombardi G, Mantero F, Martino E, Giordano G, Ghigo E. Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. *Clin Endocrinol (Oxf)* 2004;61:320-6.

### SUMMARY

**Background** Traumatic head injury and subarachnoid hemorrhage are known causes of hypopituitarism, but there are few studies in which pituitary function was systematically assessed in patients who survived either event. In this multicenter study hypothalamic-pituitary function was tested systematically in groups of these patients.

**Methods** The study subjects were 100 patients (31 women, 69 men; mean age, 37 years) who had sustained a traumatic head injury and 40 patients (26 women, 14 men; mean age, 51 years) who had sustained a subarachnoid hemorrhage from a ruptured cerebral aneurysm. The head-injury group consisted of 55 patients with a mild injury (Glasgow Coma Scale, 13 to 15), 24 with a moderate injury (Scale, 9 to 12), and 21 with a severe injury (Scale,  $\leq 8$ ).

Three months after discharge from the intensive-care unit, the patients had measurements of multiple hormones in serum or urine and urine volume. Central adrenal insufficiency was defined as a serum cortisol value  $< 8.0 \mu\text{g/dl}$  ( $220 \text{ nmol/L}$ ) and 24-hour urinary cortisol excretion  $< 30 \mu\text{g/day}$  ( $83 \text{ nmol/day}$ ); central hypothyroidism as a serum free thyroxine value  $< 0.8 \text{ ng/dl}$  ( $10 \text{ pmol/L}$ ) with a normal or low serum thyrotropin (TSH) value; central hypogonadism as normal or low serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) values and low serum testosterone (men) or serum estradiol values (women); growth hormone (GH) deficiency as a serum GH value  $< 16.5 \mu\text{g/L}$  in response to intravenous administration of GH-releasing hormone and arginine; and diabetes insipidus as a 24-hour urine volume  $> 3.5 \text{ L}$  and urine osmolality  $< 300 \text{ mOsm/kg}$ . Serum prolactin was also measured.

**Results** Thirty-five of the 100 head-injury patients (35 percent) had one or more pituitary hormone deficiencies, of whom 4 percent, 6 percent, and 25 percent, respectively, had complete, multiple, and single deficiencies (Table). All the patients with central hypothyroidism and 87.5 percent of those with central adrenal deficiency had other deficiencies. Ten percent had mild hyperprolactinemia, and 1 percent an undetectable serum prolactin value.

Table. Number (%) of Patients with Pituitary Hormone Deficiencies Three Months after Traumatic Head Injury or Subarachnoid Hemorrhage.

	ACTH Deficiency	TSH Deficiency	FSH-LH Deficiency	GH Deficiency	Diabetes Insipidus
Traumatic head injury (n=100)	8 (8)	5 (5)	17 (17)	37 (37)*	4 (4)
Subarachnoid hemorrhage (n=40)	1 (2.5)	3 (7.5)	5 (12.5)	14 (35)*	3 (7.5)

\*GH deficiency was severe (peak serum GH,  $< 9 \mu\text{g/L}$ ) in 21 patients (21 percent) in the head-injury group and 10 patients (25 percent) in the subarachnoid-hemorrhage group.

Fifteen of the 40 patients (37.5 percent) with a subarachnoid hemorrhage had one or more pituitary hormone deficiencies (Table). None had complete hypopituitarism, 10 percent had multiple deficiencies, and 27.5 percent had single deficiencies. Five percent had mild hyperprolactinemia, and 2.5 percent had an undetectable serum prolactin value.

**Conclusion** Patients who sustain a traumatic head injury or subarachnoid hemorrhage may have one or more pituitary hormone deficiencies three months later.

### COMMENTARY

This survey of head-injury and subarachnoid-hemorrhage patients not long after they had recovered from, or at least survived, their injury indicates that a substantial percentage had some abnormality in pituitary function. The frequency and types of pituitary hormone deficiencies were roughly similar in two other recent studies, one of 102 head-injury patients studied 6 to 36 months after their injury (1), and the other of 40 subarachnoid-hemorrhage patients studied 12 to 72 months later (2).

What these cross-sectional studies do not provide is information about when the deficiencies occurred and whether they have any clinical importance. Was the onset during the injury or hemorrhage, or later? Presumably it was the former. Did the patients have persistent symptoms, and, if so, could any be ascribed to the hormonal deficiencies? Might early detection and correction of any deficiencies, including GH deficiency, increase the extent of recovery or at least accelerate it. Answers to these questions might have an impact on the long-term effects of these injuries or illnesses.

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Robert D. Utiger, M.D.

## Women with hypothyroidism may need higher doses of thyroxine soon after they become pregnant

Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004;351:241-9.

### SUMMARY

**Background** Many women with hypothyroidism need higher doses of thyroxine ( $T_4$ ) when they are pregnant. However, how soon after conception the need increases and when the increase in need is greatest have not been well defined. In this study women with hypothyroidism who were being treated with  $T_4$  were studied prospectively from before conception to the end of pregnancy to determine when and by how much their need for  $T_4$  increased.

**Methods** The study subjects were 19 women, aged 27 to 40 years, who had hypothyroidism and were taking  $T_4$  and planning a pregnancy. Thirteen women had hypothyroidism caused by Hashimoto's disease or therapy for hyperthyroidism or nodular goiter, and six had thyroid carcinoma. Serum  $T_4$ , thyroid hormone-binding ratio (THBR), free  $T_4$  index, TSH, estradiol, and chorionic gonadotropin (HCG) were measured before conception, as soon as possible after the first missed menstrual period, at two-week intervals during the first trimester, and monthly thereafter until delivery. The doses of  $T_4$  were raised to maintain serum TSH values  $\leq 5.0$  mU/L in the women with hypothyroidism caused by Hashimoto's disease or previous antithyroid therapy, and to maintain values  $\leq 0.5$  mU/L in the women who had a history of thyroid carcinoma.

**Results** Among the 19 women, one had two pregnancies and three became pregnant with the aid of assisted reproduction techniques. Seventeen of the pregnancies ended at term, and three were lost at from 14 to 21 weeks.

During the pregnancies, serum THBR values decreased and remained low. Serum TSH concentrations increased initially and then returned to base line as the doses of  $T_4$  were increased, whereas serum free  $T_4$  index values did not change (Table).

	Before	10 Weeks	20 Weeks	30 Weeks	38 Weeks
Serum TSH (mU/L)	1.0 $\pm$ 1.4	4.2 $\pm$ 3.8*	2.3 $\pm$ 3.2	1.3 $\pm$ 1.5	1.0 $\pm$ 0.9
Serum free $T_4$ index	8.8 $\pm$ 1.2	7.8 $\pm$ 1.8	8.9 $\pm$ 1.5	8.5 $\pm$ 1.7	8.5 $\pm$ 1.8
Serum THBR	1.0 $\pm$ 0.1	0.8 $\pm$ 0.1	0.7 $\pm$ 0.05	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1
Dose of $T_4$ (fraction of pre-pregnancy dose)	1.0	1.3 $\pm$ 0.2*	1.5 $\pm$ 0.2*	1.5 $\pm$ 0.2	1.5 $\pm$ 0.2*

\*P<0.01, as compared with before pregnancy.

Serum TSH values exceeded the threshold values necessitating an increase in  $T_4$  dose in 16 women (85 percent); they included all 6 women with thyroid carcinoma (mean increase in dose, 48 percent; range 29 to 67) and 10 of the other 13 women (mean increase, 38 percent; range, 0 to 85 percent). The need for a higher dose of  $T_4$  was first detected between 4.4 and 16 weeks of gestation (median, 8 weeks). Overall, the increase in dose was greatest between 6 and 16 weeks, and it was during this time that the serum THBR values decreased most rapidly. As compared with before pregnancy, the mean dose of  $T_4$  was 30 percent higher at 10 weeks and 50 percent higher at 20 weeks (Table), and it remained at that level thereafter.

**Conclusion** Most women who have hypothyroidism need higher doses of  $T_4$  during pregnancy. This can occur as early as the fifth week of pregnancy. Overall, the dose may need to be increased by as much as 85 percent.

### COMMENTARY

Pregnant women need more  $T_4$  soon after conception; the increase is needed not only to compensate for the pregnancy-induced increase in serum thyroxine-binding globulin concentrations but also to provide additional  $T_4$  to meet the needs of their fetuses, as evidenced by several observations. First, deiodinases and triiodothyronine nuclear receptors are detected in fetal tissues, especially neural tissue, before the onset of fetal thyroid function. Second, iodine supplementation of pregnant women with iodine deficiency is more effective in promoting normal fetal neurodevelopment when given in the first trimester, as com-

pared with when given later. Third, hypothyroidism in pregnant women is associated with increased fetal loss and some decrease in fetal neurodevelopment.

In normal pregnant women, the additional  $T_4$  is supplied primarily by chorionic gonadotropin-mediated stimulation of the thyroid. In women with hypothyroidism, it must be supplied exogenously. However, many pregnant women do not seek obstetric evaluation soon after conception, and therefore their serum  $T_4$  concentrations may be lower and their serum TSH concentrations may be higher than optimal for several weeks, or even longer, when they do seek such care. Based on this possibil-

ity, the authors of this study recommended that these women raise their dose of  $T_4$  by approximately 30 percent as soon as they know they are pregnant, and then seek evaluation. However, some women need higher doses only after many weeks' gestation, and others need no increase at all. Given these variations, the alternative approach of advising the women to have measurements of serum TSH as soon as they suspect they are pregnant seems preferable. Either way, periodic testing should be continued until at least 20 weeks' gestation.

Robert D. Utiger, M.D.

## ***BRAF* gene mutations in papillary thyroid carcinomas can be detected in biopsy specimens**

Xing M, Tufano RP, Tufaro AP, Basaria S, Ewertz M, Rosenbaum E, Byrne PJ, Wang J, Sidransky D, Ladenson PW. Detection of *BRAF* mutation on fine needle aspiration biopsy specimens: a new diagnostic tool for papillary thyroid cancer. *J Clin Endocrinol Metab* 2004;89:2867-72.

### **SUMMARY**

**Background** Among patients with thyroid nodules, fine-needle aspiration biopsy usually provides sufficient tissue to distinguish between benign and malignant thyroid nodules on the basis of cytologic evaluation of the biopsy specimen. However, some biopsies are not diagnostic, despite the presence of many thyroid cells in the specimen. A substantial fraction of papillary carcinomas have a mutation (T1796A) in the *BRAF* gene, which codes for B-Raf kinase, a component of a signaling pathway involved in cell differentiation and growth. This study was done to determine if this mutation could be detected in biopsy specimens.

**Methods and Results** Thyroid biopsy specimens and tissue from 45 patients were analyzed for *BRAF* mutations by DNA sequencing and a colorimetric method that specifically detected the T1796A mutation. Among the 40 patients who underwent surgery, 26 had a thyroid nodule with an indeterminate biopsy, 10 had a thyroid nodule with a biopsy indicative of papillary carcinoma, 3 had a nodule with a biopsy diagnosis of benign nodule, and 1 had no biopsy. The final pathologic diagnoses were papillary carcinoma in

16 patients, follicular carcinoma in 5, Hurthle-cell carcinoma in 1, benign adenoma or hyperplastic nodule in 17, and metastatic renal carcinoma in 1. Five patients did not undergo surgery; the biopsy revealed benign thyroid cells in 4 and was indeterminate in 1.

The colorimetric mutation analysis of the biopsy specimens revealed the *BRAF* mutation in 8 of the 16 papillary carcinomas (50 percent), but in none of the benign nodules, follicular carcinomas, the Hurthle-cell carcinoma, or the metastatic renal carcinoma. The result in the indeterminate nodule of the patient not operated on was negative. The results of the DNA sequencing analysis were similar, except that the mutation was detected in only 6 of the papillary carcinomas. In separate studies of thyroid tissue, the results of the two assays were concordant in 23 tissue samples with the mutation and 68 samples without the mutation.

**Conclusion** *BRAF* gene mutations are present in some papillary carcinomas, but not in follicular or Hurthle-cell carcinomas or benign thyroid nodules, and the mutations can be detected in specimens obtained by fine-needle aspiration biopsy.

### **COMMENTARY**

This *BRAF* mutation, in which thymine is replaced by adenine at position 1796 (T1796A), results in replacement of valine by glutamic acid (V599E) in the gene product. It is the most common genetic abnormality found in papillary carcinomas, being present in approximately 50 percent of patients, as in this study. The second most common genetic abnormality, present in approximately 30 percent, is a chromosomal rearrangement leading to formation of one of several different RET/PTC fusion genes (*RET/PTC1*, *RET/PTC3*, etc.). These mutations result in constitutive activation of different cell-signaling pathways, and they do not occur together (1,2). They are highly specific for classic papillary carcinoma and its variant forms (follicular variant, tall-cell, sclerosing) (3).

It is clear from this and other studies that *BRAF* and other genetic abnormalities can be detected in thyroid cells obtained by fine-needle aspiration biopsy (3). How useful will mutation

analysis of these specimens be? When the cytologic diagnosis is papillary carcinoma, the nodule is nearly always a papillary carcinoma, but not all will have a *BRAF* mutation. Thus, the test won't help much in these patients. Among those in whom the biopsy diagnosis is indeterminate (more often called follicular tumor), the test will provide a preoperative diagnosis in only a few. Xing et al. studied 26 nodules in which the biopsy was indeterminate and the nodules were later resected. Among them, 6 were papillary carcinomas, of which 2 had the mutation. Thus, the finding of this *BRAF* mutation is, so far, a highly specific indicator of papillary carcinoma or its variants, but its sensitivity falls short of what is needed for preoperative diagnosis of patients with indeterminate biopsies, the patients for whom treatment recommendations (observation vs. thyroid lobectomy [and possible completion thyroidectomy] vs. near-total; thyroidectomy) are currently the most difficult.

Robert D. Utiger, M.D.

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## Papillary and follicular thyroid carcinomas can be distinguished from benign nodules by gene profiling

Finley DJ, Zhu B, Barden CB, Fahey TJ III. Discrimination of benign and malignant thyroid nodules by molecular profiling. *Ann Surg* 2004;240:425-37.

### SUMMARY

**Background** Most papillary carcinomas can be identified by fine-needle aspiration biopsy, but follicular carcinomas and follicular variants of papillary carcinoma cannot be distinguished from follicular adenomas or hyperplastic nodules. Furthermore, the results of biopsy, when positive for carcinoma, do not provide information about the aggressiveness of the carcinoma. This study was undertaken to determine if benign thyroid nodules could be distinguished from thyroid carcinomas by gene profiling.

**Methods** Abnormal thyroid tissue was obtained at surgery from 59 patients (50 women, 9 men; mean age, 51 years) with a thyroid nodule. The nodule was a follicular adenoma or hyperplastic nodule in 26 patients, a papillary carcinoma in 11, a follicular variant of papillary carcinoma in 13, and a follicular carcinoma in 9.

RNA was extracted from the tumors, amplified, and hybridized to 627 genes on a gene chip. After staining, the chips were scanned to detect hybridization signals. The results were analyzed by cluster analysis, which led to grouping of genes according to whether they were more than two times underexpressed or overexpressed.

**Results** As a test set, 21 benign nodules and 24 papillary (including follicular variants) and follicular carcinomas were studied. Among the 627 genes, 61 were overexpressed and 72 were underexpressed in the papillary and follicular carcinomas, as compared with the benign nodules. The profile of one follicular adenoma was similar to that of the carcinoma, and the profile of one follicular variant of papillary carcinoma was similar to that of the benign nodules. Addition of the results from 5 benign nodules and 9 carcinomas resulted in two similar, distinct groups; the profile of one follicular adenoma was similar to that of the carcinoma, and the profile of three follicular variants of papillary carcinoma was similar to that of the benign nodules. The sensitivity was 91 percent and the specificity was 96 percent for the detection of carcinoma.

**Conclusion** Different genes are activated and inactivated in benign thyroid nodules and papillary and follicular thyroid carcinomas, and the differences can be detected by gene profiling.

### COMMENTARY

Gene profiling is a powerful technique, and it should ultimately prove useful in the evaluation and treatment of patients with thyroid nodules. This study provides some preliminary information in this regard, but to some extent it overstates the case for profiling. First, two separate sets of nodules should have been evaluated, an initial test set, to determine criteria for distinguishing between benign nodules and carcinomas, and then a second validation set, in which the criteria established in the test set were applied. And the validation set should have consisted of more than 5 benign

nodules and 9 carcinomas. Second, although not explicitly stated, the results in the three types of carcinoma—papillary carcinomas, follicular variants of papillary carcinoma, and follicular carcinomas—apparently were similar. This seems rather surprising; at least papillary and follicular carcinomas might be expected to have different gene profiles.

This technique can probably be applied to biopsies. However, it may not improve identification of papillary carcinomas much, because they can be reliably identified by biopsy. However, biopsy cannot distinguish between benign nodules and other types of carcinoma. If gene analysis, whether of one (see p. 50)

or many genes, of biopsy specimens can distinguish among these types of nodules, then preoperative planning will be improved. And the need for genetic information about thyroid carcinomas should increase when drugs that destroy thyroid cancer cells become available.

Robert D. Utiger, M.D.

## Metastases of other malignant tumors are an occasional cause of thyroid nodules

Wood K, Vini L, Harmer C. Metastases to the thyroid gland: the Royal Marsden experience. *Eur J Surg Oncol* 2004; 30:583-8.

### SUMMARY

**Background** Most thyroid nodules are benign, but a few are carcinomas. Most of the latter are thyroid carcinomas, but a few are metastases of carcinomas of other organs. This study determined the clinical characteristics and outcome in patients with metastases to the thyroid gland.

**Patients and Results** From 1985 to 2002, 1016 patients were operated on for malignant tumors of the thyroid gland at the Royal Marsden Hospital, London, United Kingdom. Among them, 15 patients (1.5 percent) had tumors that were metastases of tumors of other tissues. Ten of the patients were women, and five were men. Their median age at the time of diagnosis of the thyroid metastasis was 63 years (range, 26 to 76). The presenting problem was a neck mass in 11 patients and dysphagia in 2 patients; the tumor was detected by computed tomographic imaging done to evaluate cervical lymphadenopathy in 1 patient and during a cervical lymph node resection in 1 patient.

The interval between the time of diagnosis of the primary tumor and the thyroid metastasis ranged from 0 to 15 years (median, 14 months); in 5 patients the thyroid metastasis

was the first manifestation of their malignant tumor. The primary tumor was a renal-cell carcinoma in 4 patients, and 1 patient each had breast carcinoma, melanoma, lung carcinoma, colon carcinoma, Merkel-cell carcinoma of the arm, endometrial carcinoma, bladder carcinoma, carcinoma of unknown primary site, leiomyosarcoma, liposarcoma, and paraganglioma.

Five patients had biopsies that revealed metastatic tumor, and surgery revealed the tumor to be a metastasis in 9. Four of these 9 patients had metastases to other organs, but were operated on because they had a large thyroid mass. Among the other 6 patients, 5 had metastases elsewhere when they presented with the thyroid metastasis. The other metastases were most often in the lungs, but others were in cervical, mediastinal, or retroperitoneal lymph nodes. Ten patients died 3 to 45 months after presenting with the thyroid metastasis. The remaining 5 patients were alive 3 to 84 months after thyroidectomy and chemotherapy (1 patient).

**Conclusion** In occasional patients with a thyroid nodule the nodule is a metastasis of another tumor, most often a renal-cell carcinoma.

### COMMENTARY

Some patients with nonthyroid cancers have thyroid metastases detected at the time of postmortem examination, but thyroid metastases are rarely detected before death. For example, in one study 0.5 percent of all patients who died of cancer had thyroid metastases detected postmortem (1), whereas metastatic tumor was found in the thyroid in 1.2 percent of patients undergoing thyroid surgery for cancer. In most studies, as in the study by Wood et al., metastases of renal-cell carcinoma were the most common, followed by lung and breast carcinoma (2,3). Although rare, the thyroid metastasis may be the presenting manifestation of the nonthyroid tumor, and it may be the only site of metastasis.

The fact that a thyroid nodule is a metastasis may be suspected from the patient's history or by the results of fine-needle aspiration biopsy of the nodule. The presence of clear cells suggests renal-cell carcinoma, but clear cells may be seen in biopsies of benign and malignant thyroid nodules, and occasional follicular carcinomas are composed largely of these cells.

Immunostaining for thyroglobulin should identify any clear-cell nodules of thyroid origin. Similarly, immunostaining for calcitonin (or measurement of serum calcitonin) should identify nodules that are medullary carcinomas, which may have cytologic features similar to some nonthyroid carcinomas.

Robert D. Utiger, M.D.

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## Postoperative radioactive iodine therapy may reduce the risk of recurrence of papillary and follicular carcinoma

Sawka AM, Thephamongkhon K, Brouwers M, Thabane L, Browman G, Gerstein HC. A systematic review and meta-analysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab* 2004;89:3668-76.

### SUMMARY

**Background** Most patients with papillary or follicular thyroid carcinoma are treated by thyroidectomy and then radioiodine (I-131), to destroy any remaining normal thyroid tissue (remnant ablation) and perhaps also any remaining thyroid carcinoma. This analysis was undertaken to determine if remnant ablation reduces the risk of death or recurrence in patients with thyroid carcinoma.

**Methods** The literature was searched to identify clinical trials or cohort studies of adults who had papillary (both classic and follicular variant) or follicular thyroid carcinoma, underwent bilateral thyroidectomy, and had been treated with I-131 within a year after surgery; who had been followed for at least five years; and for whom 10-year data on cancer-related deaths, local and regional recurrences, and distant metastases were reported. No clinical trials, but 267 cohort studies were found, of which 23 met the inclusion criteria. The doses of I-131 ranged from 28 to 200 mCi (1036 to 7400 MBq), but were not reported in some studies.

### Results

**Cancer Mortality** Seven studies contained data on mortality. Among them, one study of 1510 patients found a significant benefit of I-131 ablation, after adjustment for age, sex, extent of surgery, and tumor characteristics (relative risk, 0.5; mortality rates not reported). The other six studies, of 135 to 2282 patients, reported 10-year cancer-related mortality rates of from 1.3 to 15 percent, and there was no benefit of I-131 therapy. In 20 studies unadjusted for other variables, the 10-year mortality rates ranged from 0 to 23 percent among I-131-treated patients and 0 to 25 percent among those not treated (mean values for papillary carcinoma and follicular carcinoma, 2 and 10 percent, respectively).

**Any Cancer Recurrence** I-131 therapy was associated with a lower risk of recurrence in three studies, of 187 to 1599 patients (relative risk, 0.5 to 0.8, after adjustments similar to those described above), but not in three other studies of 177 to 273 patients. The pooled unadjusted 10-year recurrence rates for patients with papillary or follicular carcinoma were similar in the treated and untreated groups.

**Local and Regional Recurrence** I-131 therapy was associated with a significantly decreased adjusted risk of local or regional recurrence in three studies, of 135 to 587 patients (relative risk, 0.05, 0.3, and 0.4). The pooled unadjusted 10-year local and regional recurrence rate was lower in I-131-treated patients with either papillary or follicular carcinoma than in those not treated (768 vs. 389 patients; 4 vs. 10 percent; relative risk, 0.3).

**Distant Metastases** I-131 therapy was associated with a lower adjusted risk of distant metastases in the largest study, of 1510 patients with papillary and follicular carcinoma (relative risk not given), and in a study of 587 patients with papillary carcinoma (relative risk, 0.2), but not in one study of 135 patients with follicular carcinoma. The pooled unadjusted 10-year rate of distant metastases was lower in the I-131-treated patients with either papillary or follicular carcinoma than in those not treated (877 vs. 1079 patients; 2 vs. 4 percent; relative risk, 0.03).

**Conclusion** In patients with papillary or follicular thyroid carcinoma, I-131 therapy may reduce the frequency of local and regional recurrence and distant metastases, but does not reduce mortality.

### COMMENTARY

This is a valuable summary of the studies of I-131 ablation in patients with thyroid carcinoma. The individual studies have many inconsistencies, not to mention deficiencies, and the results had been analyzed in different ways, particularly with respect to what adjustments were made. What adjustments should be made can be debated, but there is little doubt that many hard to control factors affect recurrence and death rates. Among them, the most important may be selection for

I-131 therapy.

Notwithstanding these problems, the analysis overall suggests that I-131 ablation is beneficial in reducing the frequency of local and distant recurrences, although it does not reduce mortality. Fewer recurrences mean less anxiety; less need for diagnostic studies; and less need for more surgery, more I-131 therapy, or other therapy—in short, less morbidity.

Do patients continue to benefit from I-131 ablation, or do its benefits wane with time? The median follow-up in the longest study included in this

analysis was 17 years, and most of the analyses were for 10 years of follow-up. Some patients have very late recurrences, but it is hard to believe that the benefit of I-131 therapy will wane with time. The more immediate question is whether all patients benefit. The answer is probably no, at least among patients with very small tumors. But how small, or will tumor histology or molecular genetics prove to be better determinants of risk of recurrence than size alone?

Robert D. Utiger, M.D.

## The range of serum thyrotropin values in nearly 1000 normal adults was similar to that in smaller groups

Jensen E, Hyltoft Petersen P, Blaabjerg O, Hansen PS, Brix TH, Kyvik KO, Hegedus L. Establishment of a serum thyroid stimulating hormone (TSH) reference interval in healthy adults: the importance of environmental factors, including thyroid antibodies. *Clin Chem Lab Med* 2004;42:824-32.

### SUMMARY

**Background** Measurement of serum thyrotropin (TSH) is the most sensitive biochemical and widely used test of thyroid dysfunction. There has been debate about both the definition of the normal reference range, because serum TSH values in normal subjects are not normally distributed, and the possibility that its upper boundary is skewed upward by inclusion of patients with very mild thyroid disease, presumably caused by chronic autoimmune thyroiditis, who have serum TSH values that are just within that boundary. This study was done to establish reference intervals for serum TSH in carefully selected normal subjects.

**Methods** The starting study group consisted of self-reported healthy Danish subjects, aged 17 to 66 years, who were recruited from a cohort of monozygotic and dizygotic same- and opposite-sex twin pairs. Pregnant women and subjects with previous or current thyroid disease were excluded. Among the remainder, 90 were taking some medication, 105 had a family history of thyroid disease; 129 had a high serum concentration of antithyroid peroxidase (TPO) antibodies, antithyroglobulin (Tg) antibodies, or TSH-receptor (TSHR) antibodies; 87 had high serum concentrations of two or three of the antibodies; 34 had both a family history of thyroid disease and a high serum concentration of one or more antithyroid antibodies; and 987 (460 women, 527 men) had none of these characteristics.

Serum TSH, anti-TPO antibodies, and anti-Tg antibodies were measured by immunometric assay and TSHR antibodies by radioreceptor assay in samples collected in the morning. The current reference interval for serum TSH was 0.30 to 4.0 mU/L.

**Results** The reference interval for the 987 subjects with no risk factors for thyroid disease was 0.58 to 4.1 mU/L, with 95 percent confidence intervals of 0.55 to 0.61 mU/L for the lower limit and 3.8 to 4.2 mU/L for the upper limit. (The distribution of serum TSH values was ln-Gaussian). The distribution of the values in the women and men and in the different types of twin pairs was similar to that in all 987 subjects. The values in the subjects taking some medication were similar. As compared with the normal subjects, the distribution of the values was skewed to lower values in the 105 subjects with a family history of thyroid disease and in the 15 subjects with high serum TSHR antibody values, that in the 76 subjects with high serum anti-TPO antibody values was skewed to higher values, and that in the 38 subjects with high serum anti-Tg antibody values was similar.

**Conclusion** Serum TSH concentrations in a large group of normal adult women and men range from 0.58 to 4.1 mU/L (95 percent confidence interval), similar to reference ranges based on results from fewer, less carefully selected subjects.

### COMMENTARY

Serum TSH values are not normally distributed in normal subjects, but rather are skewed toward the upper end of the normal reference range, which is often 0.4 to 4.0 mU/L or thereabouts, with mean values of approximately 1.5 mU/L. The distribution is more normal when the values are logarithmically transformed, but even then median values tend to be lower than mean values. These findings have led to the suggestion that the upper boundary of the normal range is skewed upward by the inclusion of subjects with mild thyroid disease, as noted above. In other words, the true upper limit of the normal range might be 3.2, or even 2.8, mU/L.

This study belies that suggestion. Among the 987 normal women and men

with no personal or family history of thyroid disease and normal serum concentrations of three antithyroid antibodies, the range of serum TSH concentrations was quite similar to that described by many laboratories, few of which have defined normal subjects so carefully. The number of normal subjects studied far exceeded the 120 recommended by the National Academy of Clinical Biochemistry as the minimum necessary to establish the normal reference interval for serum TSH (1).

Furthermore, even if the normal upper reference value was lower, the additional subjects designated as having subclinical hypothyroidism because their serum TSH values were, for example 3.4 or 3.8 mU/L, would benefit little. Thyroxine therapy has little or no benefit in subjects with serum TSH concentra-

tions  $\geq 4.5$  mU/L and normal serum free thyroxine values (2), so it is hard to believe it would have any benefit in those with lower serum TSH concentrations.

Robert D. Utiger, M.D.

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## Thyroid disorders are common in patients with chronic hepatitis C

Antonelli A, Ferri C, Pampana A, Fallahi P, Nesti C, Pasquini M, Marchi S, Ferrannini E. Thyroid disorders in chronic hepatitis C. *Am J Med* 2004;117:10-13.

### SUMMARY

**Background** Some patients with chronic hepatitis C virus infection have manifestations of autoimmune thyroid disease, but whether this occurs more often than in normal subjects is not clear. In this study the frequency of thyroid disorders was evaluated in patients with hepatitis C, patients with chronic hepatitis B, and normal subjects.

**Methods** The study subjects were 630 consecutive patients with chronic hepatitis caused by hepatitis C virus infection (435 women, 195 men; mean age, 61 years), 86 patients with chronic hepatitis caused by hepatitis B virus infection (53 women, 33 men; mean age, 59 years), 389 normal subjects (250 women, 139 men; mean age, 61 years) who lived in the same area of Italy, in which iodine intake is relatively low, and 268 normal subjects (166 women, 102 men; mean age, 60 years) who lived in an area of higher iodine intake. The diagnosis of chronic hepatitis C was based on high serum concentrations of aminotransferases and anti-hepatitis C antibodies for six months, and that of chronic hepatitis B on high serum aminotransferase concentrations and the presence of hepatic B viral DNA in serum for six months. Patients with either type of hepatitis who had cirrhosis or hepatocellular carcinoma were excluded. No patient had been treated with interferon- $\alpha$ .

The study subjects underwent a complete clinical examination and had measurements of serum thyrotropin (TSH), free thyroxine ( $T_4$ ), and antithyroid peroxidase (TPO) and antithyroglobulin (Tg) antibodies.

**Results** The sex, age, and smoking history were similar in the four groups (21 to 25 percent were current smokers). The patients with chronic hepatitis C had higher mean

serum TSH and anti-TPO and anti-Tg antibody concentrations and lower mean serum free  $T_4$  concentrations than the other three groups (Table).

Serum Values	Hepatitis C (n=630)	Hepatitis B (n=86)	Normal, I-Deficient (n=389)	Normal, I-Sufficient (n=268)
TSH (mU/L)	3.2 $\pm$ 9.8*	1.7 $\pm$ 1.3	1.5 $\pm$ 3.1	1.3 $\pm$ 1.1
Free $T_4$ (ng/dl)**	0.8 $\pm$ 0.5*	0.9 $\pm$ 0.3	1.0 $\pm$ 0.3	0.9 $\pm$ 0.2
Anti-TPO Ab (U/ml)	127 $\pm$ 467*	51 $\pm$ 114	42 $\pm$ 127	47 $\pm$ 144
No. (%) with high values	132 (21%)*	11(13%)	47 (12%)	27 (10%)
Anti-Tg Ab (U/ml)	124 $\pm$ 560*	37 $\pm$ 85	38 $\pm$ 187	41 $\pm$ 186
No. (%) with high values	108 (17%*)	9 (10%)	39 (10%)	24 (9%)
TSH >4.0 mU/L	82 (13%)*	3 (4%)	12 (3%)	13 (5%)
TSH <0.3 mU/L	63 (10%)	3 (4%)	39 (10%)	19 (7%)

\*P<0.05. as compared with the other three groups.  
\*\*To convert to pmol/L, multiply by 12.9.

The serum concentrations of both antibodies were high in 57 patients (9 percent) of the patients with chronic hepatitis C, as compared with 4 to 6 percent of the patients in the other three groups. Serum anti-TPO and anti-Tg antibody concentrations were high in 35 (43 percent) and 25 (30 percent), respectively, of the 82 patients with chronic hepatitis C who had high serum TSH concentrations, but in only 87 (18 percent) and 74 (15 percent), respectively, of the 485 patients with hepatitis C who had normal serum TSH concentrations.

**Conclusion** Hypothyroidism and high serum antithyroid antibody concentrations are more common in patients with chronic hepatitis C than in patients with chronic hepatitis B or normal subjects.

### COMMENTARY

This large survey of untreated patients with chronic hepatitis C confirms that they are more likely to have high serum antithyroid antibody concentrations and hypothyroidism than are patients with chronic hepatitis B or normal subjects (1). Few details about thyroid function are given, but most patients probably had subclinical hypothyroidism. Also not given are any data relating the severity of hepatitis, viral load, or epidemiology of hepatitis C infection to thyroid autoimmunity or hypothyroidism.

Many patients with chronic hepatitis C are treated with interferon- $\alpha$ , during which approximately 10 percent have some thyroid dysfunction: silent thyroiditis, with transient hyperthyroidism fol-

lowed by transient hypothyroidism; chronic hypothyroidism alone; and Graves' hyperthyroidism (1). Female sex and high base-line serum antithyroid antibody concentrations are risk factors for the development of thyroid dysfunction during interferon- $\alpha$  therapy, and this risk may be increased by addition of ribavirin (the combination is now standard therapy). This variable response to interferon- $\alpha$  is not unique to patients with chronic hepatitis C infection, but also occurs—although less often—during interferon- $\alpha$  therapy in patients with chronic hepatitis B and various malignant diseases. Why the frequency of thyroid autoimmunity and hypothyroidism during interferon- $\alpha$  therapy is higher in patients with chronic hepatitis C than in patients with other disorders is not known, but

could be due to greater endogenous interferon- $\alpha$  production in the former.

Robert D. Utiger, M.D.

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## Serum thyroid hormone concentrations fall during acute nonthyroidal illness in thyroxine-treated patients

Wadwekar D, Kabadi UM. Thyroid hormone indices during illness in six hypothyroid subjects rendered euthyroid with levothyroxine therapy. *Exp Clin Endocrinol Diabetes* 2004;112:373-7.

### SUMMARY

**Background** Serum thyroxine ( $T_4$ ) concentrations may fall in patients with nonthyroidal illness, a change that could occur as a result of a decrease in  $T_4$  secretion, a decrease in serum protein-binding of  $T_4$ , or an increase in tissue uptake of  $T_4$ . In this study serum  $T_4$  and other thyroid hormones and thyrotropin (TSH) were measured repeatedly during a nonthyroidal illness and after recovery in patients with hypothyroidism who were taking  $T_4$ .

**Methods** The study subjects were six men aged 63 to 79 years with previously diagnosed hypothyroidism treated with 0.1 to 0.15 mg of  $T_4$  daily who were hospitalized on an intensive care unit. All had normal serum  $T_4$ ,  $T_3$ , and thyrotropin (TSH) concentrations at an outpatient visit before the onset of their acute illness. The illnesses included upper gastrointestinal bleeding, chronic obstructive lung disease, sleep apnea, cirrhosis and encephalopathy, aspiration pneumonia, and severe hyperglycemia. The men were given their usual dose of  $T_4$  during hospitalization, and in addition were given multiple drugs, but none known to alter pituitary-thyroid function.

Serum total  $T_4$ , total  $T_3$ , total reverse triiodothyronine ( $rT_3$ ), and TSH were measured at the time of admission (day 1); on days 3, 5, and 7; and 7 days after discharge (the duration of acute illness preceding hospitalization and the duration of hospitalization are not stated).

**Results** The mean serum  $T_4$  and  $T_3$  concentrations were lower on day 1 than at the time of pre-illness testing (Table). The values decreased further on day 3, and then gradually increased. The mean serum  $rT_3$  concentration was high on day 1, increased further on day 3, and then declined. The mean serum TSH concentration was lower on day 1 than at the time of pre-illness testing, decreased further on day 3, then increased to above both the pre- and post-illness values on day 7.

Table. Mean Serum Thyroid Hormone and TSH Concentrations in  $T_4$ -Treated Men before, during, and after an Acute Nonthyroidal Illness.

	Pre-Illness	Day 1	Day 3	Day 5	Day 7	Post-Illness
Serum $T_4$ ( $\mu\text{g}/\text{dl}$ )	8.4	4.2*	4.1*	5.8*	7.2	8.6
Serum $T_3$ ( $\text{ng}/\text{dl}$ )	136	73*	56*	91*	109	132
Serum $rT_3$ ( $\text{ng}/\text{dl}$ )		35*	43*	30*	18	11
Serum TSH ( $\text{mU}/\text{L}$ )	2.1	0.6*	0.4*	1.7	4.6	2.3

Normal values: serum  $T_4$ , 5 to 12  $\mu\text{g}/\text{dl}$ ;  $T_3$ , 90 to 190  $\text{ng}/\text{dl}$ ;  $rT_3$ , 5 to 16  $\text{ng}/\text{dl}$ ; and TSH, 0.4 to 4.0  $\text{mU}/\text{L}$ . Conversion factors:  $T_4$ ,  $\mu\text{g}/\text{dl} \times 12.9 = \text{nmol}/\text{L}$ ;  $T_3$  and  $rT_3$ ,  $\text{ng}/\text{dl} \times 0.015 = \text{nmol}/\text{L}$ .

\* $P < 0.01$ , as compared with post-illness value.

**Conclusion** Among patients with hypothyroidism treated with  $T_4$ , acute nonthyroidal illness resulted in a transient fall in serum  $T_4$  and  $T_3$  concentrations. Because the patients were taking  $T_4$ , the changes were probably caused by changes in  $T_4$  and  $T_3$  transport and metabolism than the concomitant decrease in serum TSH concentrations.

### COMMENTARY

The low serum TSH, total  $T_4$ , and total  $T_3$  concentrations in these  $T_4$ -treated patients mimic those in acutely ill patients with normal thyroid function. Since the patients were given  $T_4$  throughout their hospitalization, the decrease in serum total  $T_4$  concentrations cannot be ascribed to the decrease in TSH secretion, and must have been caused by a decrease in serum binding of  $T_4$  (not measured in the study). The decrease in binding may have resulted from a decrease in the serum concentrations of thyroxine-binding globulin and other thyroid hormone transport proteins (1), or the presence in serum of substances that inhibit the binding of  $T_4$  to one or more of the transport proteins. Acutely, either change would reduce serum  $T_4$  binding to protein, thereby increasing serum free  $T_4$  concentrations (also not measured) and inhibiting TSH secretion. Another

consequence of decreased serum  $T_4$  binding is an increase in  $T_4$  clearance (2), which results in a decrease in serum total  $T_4$  concentrations. Despite decreased serum  $T_4$  binding,  $T_4$  uptake into tissues and intracellular binding of  $T_4$  is impaired in acute illness (2). During recovery, normalization of serum  $T_4$  binding raises serum  $T_4$  concentrations, thereby reducing serum free  $T_4$  concentrations and transiently increasing TSH secretion. Serum  $T_3$  concentrations are low because of both decreased binding to serum proteins and decreased extrathyroidal  $T_4$  to  $T_3$  conversion.

An alternative explanation for the decrease in serum total  $T_4$  concentrations in these men is illness- or medication-related impairment in  $T_4$  absorption. However, this would be expected to decrease serum free  $T_4$  concentrations, thereby increasing TSH secretion (unless inhibited by some other component of nonthyroidal illness). The rise in serum

reverse  $T_3$  concentrations indicates there was no true  $T_4$  deficiency, because  $T_4$  is the only precursor of reverse  $T_3$ .

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## High maternal serum thyroid hormone concentrations are associated with increased fetal loss and low birth weight

Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S. Fetal loss associated with excess thyroid hormone exposure. *JAMA* 2004;292:691-5.

### SUMMARY

**Background** The effects of maternal hyperthyroidism on pregnancy and fetal development have been little studied, in contrast to those of maternal hypothyroidism. This study evaluated the effects of the high serum thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>) concentrations in women and men with the syndrome of generalized resistance to thyroid hormone on the course of pregnancy and on development and thyroid function of their offspring.

**Methods** The study subjects were 167 members of an Azorean family with resistance to thyroid hormone caused by an Arg243Gln mutation in the β isoform of the T<sub>3</sub> nuclear receptor. Among them, 44 (23 women, 21 men) carried the mutation, and 123 did not; the latter included 35 first-degree relatives (18 women, 17 men), 54 distant relatives (21 women, 33 men), and 34 relatives by marriage (14 women, 20 men). The subjects were initially identified by biochemical findings, and the diagnosis was confirmed by mutation analysis. They were interviewed and their records reviewed by investigators unaware of mutation status. All couples had pregnancies. The diagnoses of pregnancy and miscarriage were based on clinical records. Among the subjects with the mutation, the mean serum free T<sub>4</sub> index and free T<sub>3</sub> index values were high, and the mean serum thyrotropin (TSH) concentration was normal; the respective values were normal in all other subjects.

**Results** There were 18 couples in which one subject carried the Arg243Gln mutation and 18 couples of unaffected first-degree relatives. The frequency of miscarriage was considerably higher in the couples in which the woman was affected, as compared with the couples in which the man was affected, the couples of unaffected first-degree relatives, and couples of unrelated subjects living on the same island (Table).

Table. Frequency of Miscarriage among Couples in Which the Woman or Man, or Neither, Carried the Arg243Gln Mutation.

	Affected Mothers	Affected Fathers	Neither Affected	Unrelated
Couples (no.)	9	9	18	1804
Pregnancies (no.)	59	30	68	3765
Miscarriages (no.)	14	2	6	305
Rate of miscarriage per pregnancy (%)	24	7	9	8
Rate of miscarriage per couple (%)	23*	2	4	

\*P=0.01, as compared with the other groups.

The affected mothers delivered 20 affected infants and 11 unaffected infants, and the spouses of the affected men delivered 15 affected infants and 12 unaffected infants. Birth-weight data were available for approximately 80 percent of the infants in each of the four groups. The mean standard deviation (SD) of the birth-weight for gestational age was -1.8 for unaffected infants delivered by affected mothers, as compared with -0.1 for affected infants of affected mothers. The SD values in the affected and unaffected infants of affected fathers and the infants of unaffected first-degree relatives were similar to that of the infants born on the island.

Newborn screening blood-spot thyrotropin (TSH) values were birth available for 43 infants. The values were undetectable (<0.1 mU/L) in 3 unaffected infants of affected mothers, but similar (approximately 5 mU/L) in 8 affected infants of affected mothers, 13 affected or unaffected infants of affected fathers, and 19 infants of the unaffected first-degree relatives.

**Conclusion** The rate of miscarriage is high among women with high serum thyroid hormone concentrations as a result of generalized thyroid hormone resistance. Their affected infants have normal birth weight and normal serum TSH values, whereas their unaffected infants have low birth weight and low serum TSH values.

### COMMENTARY

Is the high miscarriage rate, probably mostly of unaffected fetuses, and the low birth weight and low neonatal blood-spot TSH values in unaffected infants delivered by the mothers with thyroid hormone resistance, indicative simply of the effects of high maternal serum free T<sub>4</sub> and T<sub>3</sub> values? Or are the changes somehow unique to families with thyroid hormone resistance? Affected mothers are normal by most if not all criteria

(including fertility and disorders of pregnancy such as preeclampsia and premature labor), and unaffected offspring have normal thyroid function and action. Furthermore, the outcomes are obviously independent of metabolic or fetoplacental effects of maternal hyperthyroidism or maternal Graves' disease (the most common cause of high serum free T<sub>4</sub> and T<sub>3</sub> values in pregnant women). In this instance only unaffected fetuses were exposed to the high values. Thus, high maternal serum free T<sub>4</sub> and free T<sub>3</sub> con-

centrations must be the culprit.

While the serum free T<sub>4</sub> and T<sub>3</sub> index values in the affected mothers were quite high, these results should provide a warning that overly aggressive treatment of hypothyroidism should be avoided in other pregnant women.

Robert D. Utiger, M.D.

## Radiographic contrast agents have little acute effect on pituitary-thyroid function

Gartner W, Weissel M. Do iodine-containing contrast media induce clinically relevant changes in thyroid function parameters of euthyroid patients within the first week? *Thyroid* 2004;14:521-4.

### SUMMARY

**Background** Water-soluble radiographic contrast agents contain large amounts of iodide, which has both antithyroid and prothyroid effects. Whether these agents have acute effects on thyroid function is not known. This study evaluated the immediate effects of these agents on pituitary-thyroid function in normal subjects.

**Methods** The study subjects were 22 patients (6 women, 16 men; age range, 28 to 82 years) who underwent elective coronary arteriography (16 patients) or computed tomography (6 patients), during which they received intravenous injections of a water-soluble radiographic contrast agent, in the form of iodixanol, iopamidol, or iopromid. None had a history of thyroid disease or was seriously ill, and all had normal serum thyrotropin (TSH), free thyroxine (T<sub>4</sub>), and antithyroid peroxidase antibody concentrations. Serum TSH and free T<sub>4</sub> were measured twice before and daily for seven days after contrast administration.

**Results** The total doses of iodide administered, as organic iodide, ranged from 300 to 1121 (mean, 536) mg/kg of body weight. There were no changes in mean serum free T<sub>4</sub>

concentrations, but mean serum TSH concentrations increased slightly but significantly on days 3 and 4 (Table).

Table. Mean Serum Free T<sub>4</sub> and TSH Concentrations before and after Radiographic Contrast Agent Administration.

	Day							
	0	1	2	3	4	5	6	7
Free T <sub>4</sub> (ng/dl)	1.34	1.28	1.33	1.28	1.29	1.25	1.23	1.40
TSH (mU/L)	1.23	1.39	1.79	1.99*	1.96*	2.02*	1.84	1.75

To convert free T<sub>4</sub> values to pmol/l, multiply by 12.9.  
\*P<0.05, as compared with base line.

The mean (±SD) maximal increment in serum TSH concentration was 2.4±1.7 mU/L, and four patients had values above the upper limit of the normal range at some time. There was a statistically significant correlation between base-line and peak serum TSH concentrations after contrast administration.

**Conclusion** In patients with normal thyroid function intravenous administration of a radiographic contrast agent does not acutely alter serum T<sub>4</sub> concentrations, but may cause a small transient increase in serum TSH concentrations.

### COMMENTARY

All the contrast agents used for radiography and computed tomography are iodinated organic compounds. Their iodide content is high, and since high doses (up to 200 ml) are given, the quantity of iodide given is very high, as noted above. This is nearly all organic iodide, much of which is rapidly excreted unchanged in the urine. However, these solutions also contain small amounts of inorganic iodide (2 to 20 µg/ml [1]), resulting in total doses of up to 4000 µg, and small amounts of contrast are deiodinated in vivo, further increasing the dose. Thus, the total dose of inorganic iodide may be 20 to 30 times the recommended daily intake for an adult (150 µg). The lowest dose of inorganic iodide that has effects similar to the effects found in this study is 1500 µg daily.

In most other surveys of thyroid function in patients given a radiographic contrast agent, the first measurements were done 1 week later (summarized in

2). In the largest survey, 788 patients were studied before and 1, 4, and 12 weeks after coronary angiography (3). Among them, 2 patients had overt hyperthyroidism 4 weeks later, 6 patients had overt hypothyroidism 1 week later (it was transient in 4 patients), and 2 patients had overt hypothyroidism 12 weeks later. In addition, 5 percent had subclinical hyperthyroidism at 4 weeks, and 14 percent had subclinical hypothyroidism at 4 weeks, with lower percentages at the other times (including base line).

The very small antithyroid effect of contrast-agent administration found in this study means that in most patients the results of serum TSH measurements in the first few days after the radiologic study accurately reflect their thyroid function before the study. Measurements at this time do not, however, predict later thyroid dysfunction caused by contrast administration, but that is rare.

Robert D. Utiger, M.D.

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## Dopamine, but not dobutamine or dopexamine, inhibits thyrotropin and prolactin secretion

Schilling T, Grundling M, Strang CM, Moritz KU, Siegmund W, Hachenberg T. Effects of dopexamine, dobutamine or dopamine on prolactin and thyrotropin serum concentrations in high-risk surgical patients. *Intensive Care Med* 2004;30:1127-33.

### SUMMARY

**Background** Some patients with nonthyroidal illness, particularly those in intensive-care units, have low serum thyrotropin (TSH) concentrations, which may, at least in part, be caused by drugs given to increase cardiac output. The effects of three drugs, dopamine, dobutamine, and dopexamine, given to raise cardiac output, on TSH and prolactin secretion were evaluated in this study.

**Methods** The study subjects were 30 men (age range, 39 to 74 years), who underwent elective major abdominal surgery. Twenty-six of the men also had other medical problems, such as ischemic heart disease, hypertension, and chronic lung or renal disease. One day after surgery, starting at 8 am, the men were randomly assigned to receive dopamine, dobutamine, or dopexamine for eight hours (10 men in each group). The initial dose was low, and it was increased gradually at 10-minute intervals as needed to increase cardiac output by 35 percent. The infusions were continued for a total of eight hours. Cardiac output, oxygen delivery, oxygen consumption, and serum TSH and prolactin were measured at baseline and repeatedly during the infusions, and 2 and 16 hours later.

**Results** Cardiac output increased by 36 to 38 percent, oxygen delivery by 31 to 34 percent, and oxygen consumption

by 22 to 23 percent in the three groups; the mean ( $\pm$ SD) final infusion rates were  $5.0 \pm 1.8$   $\mu\text{g}/\text{kg}/\text{min}$  for dopamine,  $4.1 \pm 1.9$   $\mu\text{g}/\text{kg}/\text{min}$  for dobutamine, and  $0.7 \pm 0.3$   $\mu\text{g}/\text{kg}/\text{min}$  for dopexamine.

In the men who received dopamine, the mean serum TSH concentration decreased from 1.1 mU/L (interquartile range, 0.2 to 1.6) to 0.3 mU/L (interquartile range, 0.1 to 0.5) in two hours. The mean values were  $<0.3$  mU/L during the remainder of the infusion, and they were similar to base line two and 16 hours after the infusion. The mean serum prolactin concentration decreased from  $13 \pm 2$   $\mu\text{g}/\text{L}$  at base line to  $4 \pm 1$   $\mu\text{g}/\text{L}$  in one hour and to  $<1$   $\mu\text{g}/\text{L}$  at two hours. It remained at this level during the rest of the infusion, was  $31 \pm 10$   $\mu\text{g}/\text{L}$  two hours after the infusion, and  $13 \pm 3$   $\mu\text{g}/\text{L}$  16 hours after the infusion. There were no changes in serum TSH or prolactin concentrations in the men given dobutamine, which has strong  $\beta_1$ -adrenergic and  $\alpha$ -adrenergic antagonist activity, but little dopaminergic activity, or dopexamine, which has strong  $\beta_2$ -adrenergic activity and weak dopaminergic activity.

**Conclusion** In postoperative surgical patients infusions of dobutamine and dopexamine in doses that increase cardiac output have little effect on TSH and prolactin secretion, whereas a dose of dopamine that has a similar cardiac effect inhibits the secretion of both hormones.

### COMMENTARY

Numerous factors decrease TSH secretion, including nonthyroidal illness, caloric deprivation, and some drugs (1). Among the latter, dopamine is the most potent. Conversely, dopamine antagonists increase TSH secretion, both in normal and acutely ill subjects. These actions are mediated via dopamine D2 receptors in the pituitary and median eminence.

In this context, Schilling and colleagues studied the effects of intravenous infusions of dopamine, dobutamine (primarily a  $\beta_1$ -adrenergic agonist), and dopexamine (primarily a  $\beta_2$ -adrenergic agonist) on TSH and prolactin secretion in men 24 hours after major abdominal surgery. The men in the three groups were well matched at base line, and equipotent cardiac doses of the drugs were administered. There were possible confounding effects of disturbed circadian variation, stress, post-operative com-

plications, and other medications, but these were minimized by the study design and similarity of groups at base line. The study results are clear. Neither dobutamine nor dopexamine had any effect on TSH or prolactin secretion. In contrast, dopamine decreased mean serum TSH concentrations within two hours, and the concentrations were at the assay detection limit thereafter. The changes in serum prolactin were similar. There was no placebo group, but there is no reason to suspect that serum TSH and prolactin concentrations would have changed in response to placebo.

These drugs are given to very sick people, some of whom already have abnormalities in serum TSH and thyroid hormone concentrations. This study makes it clear that infusions of dopamine, at a rate of 5  $\mu\text{g}/\text{kg}/\text{min}$  (a typical dose given in an intensive-care unit) or higher, lead to very low, and even undetectable, serum TSH concentrations, but

other drugs with similar cardiac effects do not. From an endocrinologists' perspective, therefore, the other drugs are preferable, because prolonged dopamine infusion would be expected to result in iatrogenic central hypothyroidism. While spontaneously occurring central hypothyroidism in patients with acute, severe illnesses may be a beneficial adaptation to illness, the even more severe central hypothyroidism induced by dopamine may not.

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## Thyronamines are naturally occurring metabolites of thyroid hormone that rapidly inhibit neural and cardiac function in animals

Scanlan TS, Suchland KL, Hart ME, Chiellini G, Huang Y, Kruzich PJ, Frascarelli S, Crossley DA II, Bunzow JR, Ronca-Testoni S, Lin ET, Hatton D, Zucchi R, Grandy DK. 3-Iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat Med* 2004;10:638-42.

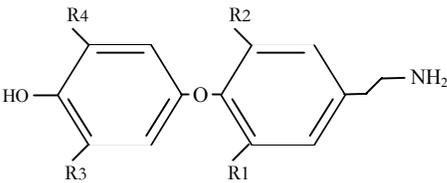
### SUMMARY

**Background** The major actions of thyroid hormone, in the form of triiodothyronine ( $T_3$ ), are to regulate the transcription of genes whose products control the growth, development, and function of many organ systems. These actions take hours or days. Some actions of thyroid hormone are rapid, and presumably nongenomic. Possible mediators of these actions are thyronamines, which are decarboxylated and deiodinated derivatives of  $T_3$ . Given their similarity to biogenic amines, thyronamines may activate amine-sensitive receptors. This study describes the actions of some iodothyronamines and their detection in animal tissues.

**Methods and Results** Thyronamine ( $T_0$ -amine) and several iodothyronamines stimulated cyclic AMP production by embryonic kidney cells transfected with type 1 trace amine receptors (TAR1), a member of a family of orphan guanine nucleotide-binding (G) protein-coupled receptors (Table). The stimulation was dose-dependent, and there was no stimulation of cells transfected with dopamine  $D_1$  receptors or  $\beta_2$ -adrenergic receptors.  $T_0$ -amine and  $T_1$ -amine did not bind to  $T_3$  receptors, and  $T_3$  and thyroxine ( $T_4$ ) did not activate TAR1 receptors.

$T_0$ -amine and  $T_1$ -amine were isolated from extracts of brain, heart, liver, and blood of mice. Administration of  $T_0$ -amine and  $T_1$ -amine to mice resulted in sudden hypothermia (temperature fall from 37°C to 29.5°C in 120 minutes),

Table. Structure and Activity of Thyronamines.



Thyronamine	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	EC <sub>50</sub> (nM)
$T_0$ -amine	H	H	H	H	131
$T_1$ -amine	I	H	H	H	14
$T_2$ -amine (3,3')	I	H	I	H	41
$T_2$ -amine (3,5)	I	I	H	H	56
$T_3$ -amine	I	I	I	H	87
$T_4$ -amine	I	I	I	I	>1000

inactivity, ptosis, and a hunched-back posture lasting 6 to 8 hours. The responses were dose-dependent, and the effective doses were similar to those of other biogenic amines. In mice,  $T_0$ -amine and  $T_1$ -amine slowed the heart rate in 10 minutes, and the effect also lasted for 6 to 8 hours. In isolated perfused rat hearts,  $T_0$ -amine and  $T_1$ -amine caused a rapid fall in heart rate and cardiac output. These decreases were reversed by addition of isoproterenol to the perfusion medium.

**Conclusion**  $T_0$ -amine and  $T_1$ -amine are naturally occurring derivatives of  $T_4$  and  $T_3$  that activate G-protein-coupled receptors and inhibit neural and cardiac activity.

### COMMENTARY

The discovery of thyronamines may be a major development in thyroidology, because it may lead to the ability to understand and eventually to control the interaction between thyroid hormone and the adrenergic nervous system. In the brain, an iodinated derivative of  $T_4$  is concentrated in all major adrenergic centers, their outflow tracts, and their synaptic terminals (1). Yet the proposed neuroactive metabolites, amine derivatives of the hormone, though long sought, had not been identified. Now, two thyronamines have been isolated from the brain, synthesized, and tested. While they have what appear to be adrenergic blocking effects, there is good reason to believe

that they represent only the first of a series of thyroid hormone-derived amines, and that others may have adrenergic activating rather than blocking properties. Moreover, the TAR1 receptor, responsive to  $T_0$ -amine and  $T_1$ -amine, and signaling robust cyclic AMP formation, is nevertheless only one of a large family of trace amine receptors that may respond to other thyronamines—with varying numbers of iodine atoms or even hydroxyl group modifications. So there is much to anticipate. In the meantime, the central nervous system and cardiac inhibitory properties of  $T_0$ -amine and  $T_1$ -amine could prove to be useful clinically, for example, in the treatment of patients with severe hyperthyroidism or possibly atrial fibrillation. Thinking more

boldly, may they even have a role in the treatment of patients with certain mental disorders?

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