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LOW SERUM THYROTROPIN CONCENTRATIONS AS A RISK FACTOR FOR ATRIAL FIBRILLATION IN OLDER PERSONS

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Abstract *Background.* Low serum thyrotropin concentrations are a sensitive indicator of hyperthyroidism but can also occur in persons who have no clinical manifestations of the disorder. We studied whether low serum thyrotropin concentrations in clinically euthyroid older persons are a risk factor for subsequent atrial fibrillation.

Methods. We studied 2007 persons (814 men and 1193 women) 60 years of age or older who did not have atrial fibrillation in order to determine the frequency of this arrhythmia during a 10-year follow-up period. The subjects were classified according to their serum thyrotropin concentrations: those with low values (≤0.1 mU per liter; 61 subjects); those with slightly low values (>0.1 to 0.4 mU per liter; 187 subjects); those with normal values (>0.4 to 5.0 mU per liter; 1576 subjects); and those with high values (>5.0 mU per liter; 183 subjects).

Results. During the 10-year follow-up period, atrial fibrillation occurred in 13 persons with low initial values for serum thyrotropin, 23 with slightly low values, 133 with normal values, and 23 with high values. The cumulative incidence of atrial fibrillation at 10 years was 28 percent among the subjects with low serum thyrotropin values (≤0.1 mU per liter), as compared with 11 percent among those with normal values; the age-adjusted incidence of atrial fibrillation was 28 per 1000 person-years among those with low values and 10 per 1000 person-years among those with normal values ($P = 0.005$). After adjustment for other known risk factors, the relative risk of atrial fibrillation in elderly subjects with low serum thyrotropin concentrations, as compared with those with normal concentrations, was 3.1 (95 percent confidence interval, 1.7 to 5.5; $P<0.001$). The 10-year incidence of atrial fibrillation in the groups with slightly low and high serum thyrotropin values was not significantly different from that in the group with normal values.

Conclusions. Among people 60 years of age or older, a low serum thyrotropin concentration is associated with a threefold higher risk that atrial fibrillation will develop in the subsequent decade. (N Engl J Med 1994;331:1249-52.)

ATRIAL fibrillation is a well-known manifestation of hyperthyroidism. Among older people, in whom atrial fibrillation is common,[1-4] hyperthyroidism is relatively uncommon, however.[5-7] Thus, although hyperthyroidism is a risk factor for atrial fibrillation, most older people with atrial fibrillation do not have hyperthyroidism.[8,9] Subclinical hyperthyroidism, defined as a low serum thyrotropin concentration in an asymptomatic person with normal serum thyroid hormone concentrations, is more common among older persons than overt hyperthyroidism. For example, after patients taking thyroid hormone have been excluded, low serum thyrotropin concentrations have been found in 0.9 to 1.9 percent of older persons, few of whom were judged to have clinical hyperthyroidism.[10-15]

Whether people with subclinical hyperthyroidism have an increased risk of atrial fibrillation is unknown. Because atrial fibrillation is an independent risk factor for stroke and can decrease cardiac output, it is important to identify any factors that predispose patients to have this arrhythmia. To assess this risk we examined prospectively the incidence of atrial fibrillation in relation to serum thyrotropin concentrations over 10 years among older people (more than 60 years of age) who were participating in the Framingham Heart Study.

METHODS

We studied all the members of the original cohort of the Framingham Heart Study who were 60 years of age or older at the time of the 15th biennial examination in 1978 through 1980. Those who had atrial fibrillation at that time or had a history of the arrhythmia were excluded, as were two subjects found to have clinical hyperthyroidism at that examination. Subjects who did not return for any follow-up examinations after the 15th examination were also excluded. We reviewed the records of the remaining 2007 persons (814 men and 1193 women) to determine whether they were taking a thyroid hormone preparation at the time of the 15th examination and to identify atrial fibrillation occurring during the next 10 years. The 60 subjects with a history of hyperthyroidism before the

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15th examination and the 115 subjects who were taking a thyroid hormone preparation at that time were included. Those with a history of hyperthyroidism had been treated with surgery (23 subjects), antithyroid drugs (15 subjects), radioiodine (13 subjects), or iodine (5 subjects); had not been treated (1 subject); or their treatment was unknown (3 subjects). A total of 1048 of the men and women studied at the 15th examination returned for the 20th examination; 648 persons had died in the interim, and the other 311 had returned for one or more of the intervening examinations.

Serum samples were collected during the 15th examination and stored at −20°C. Serum thyrotropin concentrations were measured in 1990 and 1991 with a chemoluminescence assay (London Diagnostics, Eden Prairie, Minn.; this assay is now made by Nichols Institute Diagnostics, San Juan Capistrano, Calif.); the sensitivity of the assay was 0.005 mU per liter, and the interassay coefficient of variation was 5 percent at 1 mU per liter and 11 percent at 0.04 mU per liter. Serum thyrotropin concentrations had been measured in 1981 through 1983 with an older radioimmunoassay.[16] The mean of the serum thyrotropin concentrations that were greater than 5 mU per liter and less than or equal to 10 mU per liter was 6.8 mU per liter when measured by the older assay and 6.7 mU per liter by the newer assay; for values above 10 mU per liter, the means were 17.9 mU per liter and 16.8 mU per liter, respectively. The correlation coefficient of the two assays for values above 5 mU per liter was 0.91. These results indicate the stability of serum thyrotropin concentrations measured in frozen serum samples. For the newer assay, the normal range of serum thyrotropin values in younger adults was from >0.4 to 5.0 mU per liter.

Serum thyroxine concentrations were measured in 1981 through 1983 by radioimmunoassay (Diagnostic Products, Los Angeles); the normal range was 4.7 to 12.0 μg per deciliter (60 to 154 nmol per liter). Sixty-five persons (52 women and 13 men) were taking estrogen at the time of the 15th examination; among those taking estrogen who had normal serum thyrotropin concentrations and were not taking a thyroid hormone preparation, the mean serum thyroxine concentration was 7.6 μg per deciliter (98 nmol per liter), indicating that the estrogen therapy had little effect on the serum thyroxine concentration. All assays were done singly, except those on samples with values outside the normal range, which were reassayed in duplicate.

In our analyses, the subjects were divided into four groups according to their serum thyrotropin values: those with values ≤0.1 mU per liter (low values); those with values >0.1 to 0.4 mU per liter (slightly low values); those with values >0.4 to 5.0 mU per liter (normal values); and those with values >5.0 mU per liter (high values). These categories were based on the normal range and the likelihood that a serum thyrotropin value of 0.1 mU per liter or less is indicative of hyperthyroidism. With this thyrotropin assay, most patients with clinically evident hyperthyroidism had serum thyrotropin concentrations below 0.05 mU per liter and none had a concentration above 0.1 mU per liter.[17]

Atrial fibrillation was diagnosed by electrocardiography performed at the biennial examinations and during any intervening hospitalizations during the 10 years of follow-up, after review of the records by two cardiologists; the date of onset was considered to be the date of the first electrocardiographic documentation of atrial fibrillation. The incidence of atrial fibrillation during the 10-year follow-up period, adjusted by the direct method for the age distribution of the full cohort at the 15th biennial examination, was calculated for each group according to the Kaplan–Meier technique.[18] Proportional-hazards analysis[19] was used to test the association of the serum thyrotropin groups with the incidence of atrial fibrillation after adjustment for age.

A multivariate model was also computed to control for other known risk factors for atrial fibrillation that were present at the 15th examination (smoking, diabetes mellitus, hypertension, left ventricular hypertrophy, myocardial infarction, congestive heart failure, and heart murmur). The results are expressed as rates per 1000 person-years of follow-up or as relative risks, with 95 percent confidence intervals, for the group in question, with the group with normal serum thyrotropin concentrations as the reference group.[20] Calculations were performed for all subjects together and also after the exclusion of those taking thyroid hormone preparations at the 15th examination and those with a history of hyperthyroidism before 1978 through 1980. All P values are based on a two-tailed analysis.

Results

Incidence of Atrial Fibrillation

During the 10-year follow-up period, atrial fibrillation developed in 192 persons. The overall age-adjusted rate was 12 per 1000 person-years (Table 1).

Initial Serum Thyrotropin Concentrations and Incidence of Atrial Fibrillation

Among the subjects with low serum thyrotropin concentrations (≤0.1 mU per liter) in 1978 through 1980, the cumulative incidence of atrial fibrillation after 10 years was 28 percent (Fig. 1); the comparable rates in the other groups were 16 percent in the group with slightly low serum thyrotropin values, 11 percent in the group with normal values, and 15 percent in the group with high values. The age-adjusted rate of atrial fibrillation in the group with low serum thyrotropin concentrations was significantly higher than that in the group with normal concentrations (P = 0.005) (Table 1). There was a nonsignificant trend in the same direction for the slightly-low-serum-thyrotropin and high-serum-thyrotropin groups.

When the results were adjusted for age and sex and for the presence of other known risk factors for atrial fibrillation, including smoking, diabetes mellitus, hypertension, left ventricular hypertrophy, myocardial infarction, congestive heart failure, and cardiac murmur, the relative risk of new atrial fibrillation in those in the low-serum-thyrotropin group was 3.1 (95 percent confidence interval, 1.7 to 5.5), significantly different (P<0.001) from that in the normal-serum-thyrotropin group (Table 2). After adjustments, the subjects who had slightly low serum thyrotropin concentrations also had a somewhat higher risk than those with normal concentrations (relative risk, 1.6; P = 0.05). Excluding the subjects receiving thyroid hormone therapy at the 15th examination had only a limited effect on the relative risk in any of the groups with abnormal serum thyrotropin concentrations (Table 2). Furthermore, the exclusion of those who had had hyperthyroidism had no effect when the low-serum-thyrotropin group was compared with the normal-serum-thyrotropin group (relative risk, 2.4; 95 percent confidence interval, 1.3 to 4.8; P = 0.007).

Relation of Serum Thyroxine to Serum Thyrotropin and Subsequent Atrial Fibrillation

Subjects in the low-serum-thyrotropin group had a significantly higher mean (±SD) serum thyroxine concentration (8.9±2.4 μg per deciliter [115±31 nmol per liter]) than those in the normal-serum-thyrotropin group (7.3±1.7 μg per deciliter [94±22 nmol per liter]; P = 0.001) at the 15th examination. Among the 25 persons in the low-serum-thyrotropin group who were not taking thyroid hormone, the serum thyroxine concentration was within the normal range in 21. There was no relation between the serum thyroxine concentration and the subsequent occurrence of atrial fibrillation in the study group as a whole (P = 0.71 with adjustment for age; P = 0.60 with adjustment for age and risk factors). After adjustment for the serum thyroxine concentration, the relative risk of atrial fi-

brillation in the subjects in the low-serum-thyrotropin group was 3.0 (95 percent confidence interval, 1.7 to 5.5; P<0.001).

Clinical Hyperthyroidism and Thyroid Hormone Treatment in Subjects in Whom Atrial Fibrillation Developed

Among the 13 persons in the low-serum-thyrotropin group who had atrial fibrillation during the 10-year follow-up period, only 2 had clinical hyperthyroidism during the same period. In only one of them, who had a recurrence of Graves' hyperthyroidism that had previously been successfully treated, did the hyperthyroidism appear at the same time as atrial fibrillation. This person was also the only 1 of the 13 who had a serum thyroxine concentration above 10 μg per deciliter (129 nmol per liter) at the 15th examination; her serum thyroxine concentration at this time was 14.4 μg per deciliter (185 nmol per liter). The other person who later had hyperthyroidism had a serum thyroxine concentration of 10.0 μg per deciliter (129 nmol per liter) at the 15th examination. In four other subjects, two in the low-serum-thyrotropin group and one each in the slightly-low- and normal-serum-thyrotropin groups, hyperthyroidism developed after the 15th examination, but they did not have atrial fibrillation during the follow-up period.

Table 1. Serum Thyrotropin Concentrations in 1978 through 1980 and Incidence of Atrial Fibrillation (AF) in the Next 10 Years.

Serum Thyrotropin Value	No. at Risk	Sex (M/F)	No. with AF	Rate of AF (per 1000 Person-Years)*	P Value†
Low (≤0.1 mU/liter)	61	8/53	13	28	0.005
Slightly low (>0.1 to 0.4 mU/liter)	187	84/103	23	16	0.11
Normal (>0.4 to 5.0 mU/liter)	1576	680/896	133	11	—
High (>5.0 mU/liter)	183	42/141	23	15	0.08
All subjects	2007	814/1193	192	12	—

*The age-adjusted incidence per 1000 person-years of follow-up.

†For the comparison with the rate in the group with the normal serum thyrotropin values.

Overall, only 2 of the 192 subjects who had atrial fibrillation also had spontaneous hyperthyroidism; both of them had low serum thyrotropin concentrations at the 15th examination. Four of the 57 subjects who began taking thyroid hormone during the follow-up period also had atrial fibrillation, 3 of whom were among the 28 subjects in the high-serum-thyrotropin group who began taking thyroid therapy during this period.

Low Serum Thyrotropin Concentrations in Subjects without Atrial Fibrillation

Forty-six subjects in the low-serum-thyrotropin group did not have either atrial fibrillation or overt hyperthyroidism during the follow-up period. Thirty of the 46 were taking thyroid hormone at the time of the 15th examination. No further data on serum thyrotropin concentrations were available for 10 of the 46. Among the remaining 36 subjects, 19 had serum thyrotropin concentrations of 0.1 mU per liter or lower on at least one subsequent occasion and 6 others had concentrations of 0.2 mU per liter or lower at least once; 19 also had at least one subsequent serum thyrotropin concentration within the normal range.

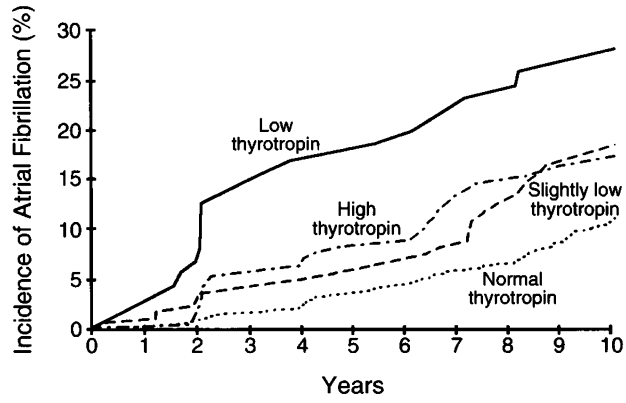

Figure 1. Cumulative Incidence of Atrial Fibrillation among Subjects 60 Years of Age or Older, According to Serum Thyrotropin Values at Base Line.

Low serum thyrotropin values were defined as ≤0.1 mU per liter; slightly low values, >0.1 to 0.4 mU per liter; normal, >0.4 to 5.0 mU per liter; and high, >5.0 mU per liter.

Discussion

The sensitive assays for serum thyrotropin[21] now available make it possible to distinguish normal from subnormal values and to identify degrees of suppression of thyrotropin secretion. Persons with low serum concentrations of thyrotropin but no clinical manifestations of hyperthyroidism can be followed for the manifestations (such as atrial fibrillation) that are usually associated with overt hyperthyroidism. In our study we found that a low serum thyrotropin concentration (≤0.1 mU per liter) in persons 60 years of age or older was an independent risk factor for atrial fibrillation.

Table 2. Serum Thyrotropin Concentrations in 1978 through 1980 and Relative Risk of Atrial Fibrillation, with and without the Exclusion of Subjects Receiving Thyroid Hormone Therapy.*

Serum Thyrotropin Value	All Subjects				Excluding Subjects Receiving Thyroid Hormone			
	No. at Risk	Sex (M/F)	Relative Risk (95% CI)*	P Value	No. at Risk	Sex (M/F)	Relative Risk (95% CI)*	P Value
Low (≤0.1 mU/liter)	61	8/53	3.1 (1.7–5.5)	<0.001	25	5/20	3.8 (1.7–8.3)	<0.001
Slightly low (>0.1 to 0.4 mU/liter)	187	84/103	1.6 (1.0–2.5)	0.05	168	80/88	1.6 (1.0–2.5)	0.04
Normal (>0.4 to 5.0 mU/liter)	1576	680/896	1.0	—	1530	674/856	1.0	—
High (>5.0 mU/liter)	183	42/141	1.4 (0.9–2.3)	0.12	169	40/129	1.6 (1.0–2.4)	0.06

*Adjusted for other risk factors for atrial fibrillation (see the Results section). The subjects with normal serum thyrotropin values were the reference group. CI denotes confidence interval.

In previous studies the prevalence of atrial fibrillation at the time of the diagnosis of overt hyperthyroidism ranged from 2 to 30 percent[22-25]; the prevalence is higher among patients more than 60 years of age than among younger patients.[23-28] Few studies, however, have examined the relation between low serum thyrotropin concentrations and the subsequent development of atrial fibrillation. In one study, based on serum samples obtained from a central reference laboratory, atrial fibrillation developed in 3 of 32 subjects with subclinical hyperthyroidism during two years of follow-up, as compared with none of 35 with normal serum thyrotropin concentrations.[27] In another study, there was an increased risk of unspecified ischemic heart disease in hospitalized patients who had been taking thyroxine, but this risk was not related to the serum thyrotropin concentration and was significant only for patients younger than 65 years of age.[29] Our finding that a low serum thyrotropin concentration was a risk factor for atrial fibrillation was based on data from a large, unselected, community-based population of older persons followed for up to 10 years.

The mean serum thyroxine concentration was higher among the subjects with low serum thyrotropin concentrations than among those with normal serum thyrotropin concentrations, although in most the values were within the normal range. There was no relation between the serum thyroxine concentration and the later development of atrial fibrillation — an observation that is probably related to the large variation in serum thyroxine concentrations in the general population and to the variation in cardiac sensitivity to thyroxine.

Approximately 10 to 15 percent of patients with overt hyperthyroidism who have atrial fibrillation have an arterial embolic event.[30,31] Hence, the identification of risk factors for atrial fibrillation is important. A low serum thyrotropin concentration — that is, subclinical hyperthyroidism — appears to be one such factor. Thyroid secretion need not increase much, if at all, for atrial fibrillation to occur. Only two of the subjects in this study who had low serum thyrotropin concentrations and subsequently had atrial fibrillation also had overt hyperthyroidism during the follow-up period. Exclusion from the analysis of those with a history of hyperthyroidism or those taking thyroid hormone at the 15th examination had little effect on the results. Overall, when atrial fibrillation occurs, there is only rarely either concurrent or subsequent overt hyperthyroidism; it is more commonly associated with subclinical hyperthyroidism, which can occur either spontaneously or in association with thyroid hormone therapy.

Older persons with low serum concentrations of thyrotropin should be followed for the development of overt hyperthyroidism and atrial fibrillation.[32] Whether antithyroid treatment can prevent atrial fibrillation in such persons is not known. Among those who are receiving thyroid hormone and have low serum thyrotropin concentrations, the risk of atrial fibrillation can be lessened by avoiding excessively high doses.

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