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Prospective Study of the Spontaneous Course of Subclinical Hypothyroidism: Prognostic Value of Thyrotropin, Thyroid Reserve, and Thyroid Antibodies

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Subclinical hypothyroidism is a frequent syndrome affecting about 10 million people in the United States. The management of such patients is open to debate. In a long-term prospective study we analyzed the spontaneous course and the value of predictive factors in the development of overt thyroid failure. We studied 82 female patients with subclinical hypothyroidism prospectively over a mean observation period of 9.2 yr. TSH, thyroid hormones, thyroid reserve after TRH administration, thyroid antibodies, and clinical parameters were assessed at yearly intervals. The cumulative incidence of overt hypothyroidism was calculated using life-table analysis and Kaplan-Meier curves. According to the initial serum TSH concentrations (TSH, 4–6/>6–12/>12 mU/liter), Kaplan-Meier estimates of the incidence of overt hypothyroidism were 0%, 42.8%, and 76.9%, respectively, after 10 yr ($P < 0.0001$). When only patients with TSH levels greater than 6 mU/liter were analyzed, the cumulative incidence was 55.3%. The incidence of overt hypothyroidism increased in patients with impaired thyroid reserve (52.6% *vs.* 38.1%; $P = 0.05$) and positive microsomal antibodies (58.5% *vs.* 23.2%; $P = 0.03$).

This prospective long-term study demonstrates that only a part of the cohort of patients with subclinical hypothyroidism develops overt hypothyroidism over time and that a major group remains in the subclinical state after 10 yr. The measurement of TSH, microsomal (thyroperoxidase) antibodies, and thyroid reserve allows initial risk stratification for the development of overt thyroid failure (risk ratio ranging from 1.0–15.6). Our study helps to recognize the spontaneous course of subclinical hypothyroidism and in the identification of patients most likely to progress to overt hypothyroidism. (*J Clin Endocrinol Metab* 87: 3221–3226, 2002)

SUBCLINICAL HYPOTHYROIDISM is defined by elevated TSH secretion in the presence of normal concentrations of circulating thyroid hormones (1–4). This syndrome affects approximately 10 million people in the United States and is most prevalent in elderly women (5). If TSH screening were carried out, especially in elderly women, patients with subclinical hypothyroidism will be detected more frequently in the future (6, 7). As these patients have no or only minimal symptoms, the clinical relevance of this biochemical finding is controversial (1–3). Subclinical hypothyroidism has been associated with an increased risk for coronary and other heart disease and peripheral arterial disease (8–11), depression (12), and various biochemical abnormalities, including elevated low density lipoprotein cholesterol (8, 13, 14), increased serum PRL concentrations (14), and negative influence on the hemostatic profile (15). In addition, the major concern in patients with subclinical hypothyroidism is the development of overt hypothyroidism [serum T_4 and free T_4 (fT_4) below the normal range] over time.

Because of the high prevalence of this syndrome and its potential cost implications for the health care system, it is very important to determine the spontaneous course of subclinical hypothyroidism. The early detection of patients who might progress to overt hypothyroidism would be important. In the present study we studied 82 patients with subclinical hypothyroidism over a mean period of 9.2 yr. The aim of the study was to investigate the spontaneous course of subclinical hypothyroidism and the development of overt hypothyroidism to identify risk factors enhancing the occurrence of overt thyroid failure, which should have implications for the follow-up and management of patients with subclinical hypothyroidism.

Abbreviations: fT_3, Free T_3; fT_4, free T_4; FT_4I, free T_4 index; TT_3, total T_3; TT_4, total T_4.

Subjects and Methods

The study was approved by the ethics committee for human studies of the University Hospital Basel, and informed consent was given by each patient.

Patients

Between 1979 and 1999, 82 patients with subclinical hypothyroidism were followed prospectively and analyzed at the Thyroid Research Unit of our Division of Endocrinology. Only women were studied to exclude laboratory variations due to sex. The mean observation period was 9.2 yr (range, 0.5–26.3). The minimal time after radioiodine therapy or thyroidectomy before entering the study was 1 yr. Further inclusion criteria consisted of good general health, as assessed by a full medical and endocrine workup. No patients were ingesting medications that interfere with thyroid function. The underlying thyroid disorders leading to subclinical hypothyroidism consisted of Graves' disease (n = 42; 32 treated with radioiodine and 10 with surgery), autoimmune thyroiditis (n = 29; 2 had surgery and 27 were untreated), and nontoxic goiter (n = 11; all had surgery). Graves' disease was diagnosed by elevated TSH receptor antibodies and the demonstration of homogeneous thyroid tissue on ultrasound; autoimmune thyroiditis by positive thyroid peroxidase and/or thyroglobulin antibodies; and simple goiter by clin-

ical palpation and ultrasound, excluding thyroid carcinoma by cytological evaluation in patients with solitary and dominant nodules and after exclusion of other forms of goiter. In 32 patients (all with Graves' disease) radioactive iodide treatment was performed before the study. The median interval before entering the study was 7.2 yr (range, 1–28 yr). The mean dose of radioactive iodide per patient was 6.2 ± 0.5 mCi (range, 3.5–16.0 mCi). The observation period ended when patients developed overt hypothyroidism or were treated with thyroid hormones for clinical reasons (endocrine ophthalmopathy, prevention of goiter after thyroidectomy, depression, hypercholesterolemia, or infertility). The mean age of the patients was 50.7 ± 1.4 yr at entrance into the study. The diagnosis of subclinical hypothyroidism was based on elevated serum TSH concentrations (basal, >4.0 mU/liter) and normal serum concentrations of fT_4, total T_4 (TT_4), and total triiodothyronine (TT_3). All of these tests were repeated at an interval of 1 month before entering the study to prove steady state and to exclude assay variation or spontaneous fluctuations. Nearly 20% of the patients referred for the study could not be included because of normalization of TSH levels. Follow-up studies were carried out at regular annual intervals and included full medical and endocrine (14, 16) evaluations (Table 1). The entire cohort was divided into 3 subgroups according to the grade of severity of subclinical hypothyroidism based on initial serum TSH levels: grade I: TSH, 4–6 mU/liter (n = 21); grade II: TSH, more than 6–12 mU/liter (n = 36); and grade III: TSH, more than 12 mU/liter (n = 25). Overt hypothyroidism was defined by diminished concentrations of fT_4, TT_4, and fT_4 index (FTI) and elevated serum TSH concentrations (>20 mU/liter) measured on 2 different occasions. Patients presenting with minimal subclinical hypothyroidism (grade 0; basal TSH level within the reference range, but exaggerated TSH response after oral TRH stimulation) were analyzed separately (n = 29).

Hormone and antibody measurements

fT_4 (reference range, 8.5–27.0 pmol/liter) was measured by saturation analysis (Clinical Assays, Cambridge, NH). TT_4 (reference range, 55.0–158.0 nmol/liter) and TT_3 (reference range, 0.9–3.0 nmol/liter) were measured by RIA as previously described (Clinical Assays) (4, 14). T_3 uptake was measured by a routine method, and the fT_4I was calculated by multiplication of the T_4 concentration by the T_3 uptake result. Serum TSH concentrations (reference range, 0.1–4.0 mU/liter) were measured by immunoradiometric assay (TSH-RIA-gnost, Behring, Frankfurt, Germany). Before its introduction in 1990, we used RIA (correlation with the immunoradiometric assay: r = 0.93; $P < 0.0001$; n = 94). Antithyroglobulin and antimicrosomal (thyroperoxidase) antibodies were assessed using the Wellcome hemagglutination assay or the radioligand assay (Biodata anti-HGT, anti-TMS Bridge Kit, Serono). The two methods correlated significantly (r = 0.78 and 0.66, respectively; $P < 0.001$) as previously described (17).

Oral TRH test: evaluation of TSH and thyroid reserve

To evaluate pituitary TSH and thyroid reserve, oral TRH tests were carried out. TRH (Roche, Basel, Switzerland) was given at a dose of 40 mg after an overnight fast. Blood was drawn at 0 and 3 h for the measurement of TSH, fT_4, and TT_3. Thyroid reserve was then calculated by the increase in serum TT_3 3 h after TRH (normal response, >0.5 nmol/liter) (4, 14, 18). Oral TRH is not commercially available in the U.S. and, therefore, is not often used there. The oral TRH test, however, has been well standardized and reported in American literature (4, 14, 18, 19).

Statistical analysis

Data are given as the mean ± SEM. Results are presented as Kaplan-Meier curves, and the significance level was tested using the log-rank test (Fig. 1). Significant factors were calculated in a multivariate Cox proportional hazards model for the calculation of risk estimates (20). Differences in frequencies were tested with the χ^2 test or Fisher's exact test, as appropriate. Two-group comparisons were assessed by unpaired (two-sided) *t* test. Significance was defined as $P \leq 0.05$. Data were analyzed using SPSS for Windows (version 10.0, SPSS, Inc., Chicago, IL).

TABLE 1. Characteristics of the study population at study entry and at the end of the study (mean ± SEM)

	Whole cohort (n = 82)		Grade I (n = 21)		Grade II (n = 36)		Grade III (n = 25)	
	Entry	End	Entry	End	Entry	End	Entry	End
TSH (0.1–4.0 mU/liter)	12.0 ± 1.1	18.9 ± 2.7	5.0 ± 0.2	6.0 ± 0.8	8.6 ± 0.3	15.9 ± 2.3	22.9 ± 2.4	34.1 ± 7.2
fT_4 (8.5–27.0 pmol/liter)	12.3 ± 0.3	11.2 ± 0.4	13.3 ± 0.6	13.7 ± 0.7	12.6 ± 0.5	11.3 ± 0.6	10.9 ± 0.5	8.7 ± 0.6
TT_3 (0.9–3.0 nmol/liter)	1.8 ± 0.1	1.7 ± 0.0	1.7 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	1.5 ± 0.1
MAB, n (%)								
Negative	40 (48.8%)	53 (64.6%)	13 (61.9%)	16 (76.2%)	19 (52.8%)	27 (75.0%)	8 (32.0%)	10 (40.0%)
1–10 × normal	22 (26.8%)	19 (23.2%)	5 (23.8%)	3 (14.3%)	9 (25.0%)	7 (19.5%)	8 (32.0%)	9 (36.0%)
>10 × normal	20 (24.4%)	10 (12.2%)	3 (14.3%)	2 (9.5%)	8 (22.2%)	2 (5.5%)	9 (36.0%)	6 (24.0%)
Total cholesterol (3.0–5.2 mmol/liter)	5.9 ± 0.1	6.1 ± 0.1	5.7 ± 0.2	5.7 ± 0.2	5.9 ± 0.2	6.1 ± 0.2	6.1 ± 0.2	6.5 ± 0.2
LDL-cholesterol (1.6–3.4 mmol/liter)	3.8 ± 0.1	4.0 ± 0.2	3.7 ± 0.2	3.4 ± 0.3	3.9 ± 0.2	4.0 ± 0.2	4.0 ± 0.2	4.3 ± 0.2
HDL-cholesterol (0.9–2.2 mmol/liter)	1.4 ± 0.0	1.5 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.5 ± 0.0	1.4 ± 0.1
Triglycerides (0.5–2.3 mmol/liter)	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.0 ± 0.1	1.1 ± 0.1
CPK (40.0–150.0 U/liter)	95.6 ± 8.2	93.2 ± 4.6	111.1 ± 13.6	90.1 ± 6.2	88.7 ± 15.2	87.2 ± 6.7	92.5 ± 11.8	106.3 ± 11.1
BMI (20–25 kg/m^2)	24.7 ± 0.5	25.6 ± 0.5	24.8 ± 1.1	26.8 ± 1.1	25.3 ± 0.7	26.1 ± 0.8	23.7 ± 0.7	24.1 ± 0.8
Billewicz score (hypothyroid >24 points)	−18.0 ± 1.9	−19.2 ± 2.0	−18.1 ± 3.0	−21.6 ± 3.1	−18.5 ± 3.1	−21.7 ± 3.2	−17.1 ± 3.9	−13.4 ± 3.7
Zulewski score (hypothyroid >5 points)	3.1 ± 0.2	2.7 ± 0.2	3.1 ± 0.3	2.2 ± 0.3	3.1 ± 0.3	2.6 ± 0.3	3.1 ± 0.4	3.4 ± 0.3
ART (<420 msec)	375.3 ± 4.5	384.1 ± 5.4	377.5 ± 9.1	368.9 ± 9.0	370.2 ± 6.5	381.0 ± 8.0	381.4 ± 8.5	402.4 ± 10.2
Smoking, n (%)	17 (20.7%)		2 (9.5%)		6 (16.6%)		9 (36.0%)	

MAB, Microsomal antibodies; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CPK, creatinine phosphate kinase; BMI, body mass index; ART, ankle reflex time.

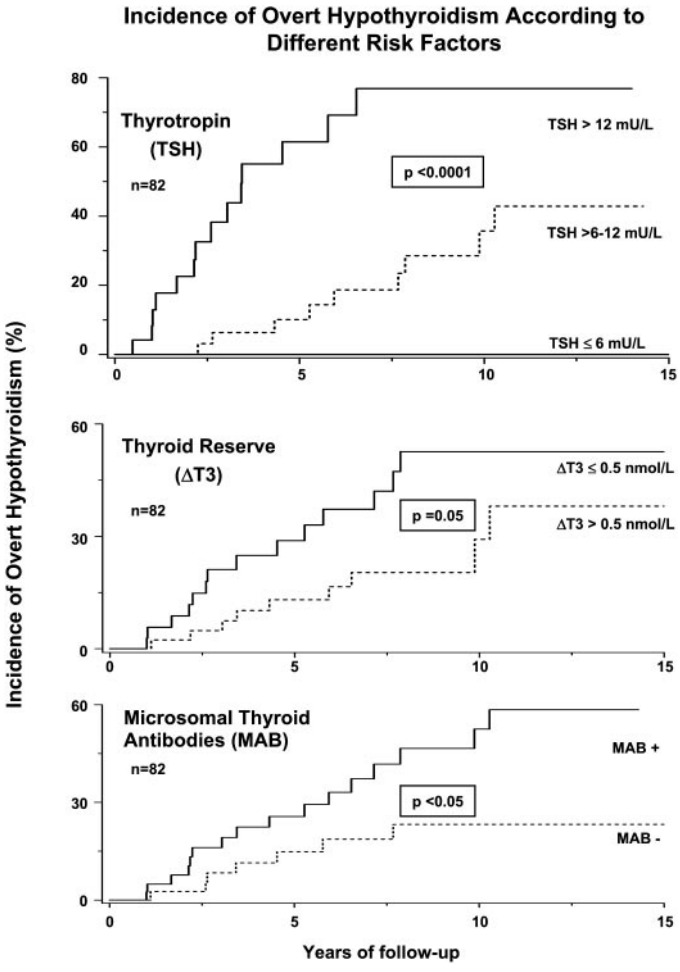

FIG. 1. Kaplan-Meier estimates of the incidence of overt hypothyroidism according to the three risk factors: TSH, thyroid reserve [increase in T_3 (δ T_3)], and microsomal antibodies (MAB). Natural course of subclinical hypothyroidism in female patients: prognostic value of TSH, thyroid reserve, and MAB. The calculated annual rate of developing overt hypothyroidism in all patients with TSH levels greater than 6 mU/liter was 5.6 ± 1.2%/yr and 3.3 ± 1.5% for grade II and 11.4 ± 3.0% for grade III.

Results

Spontaneous course of subclinical hypothyroidism

The clinical and biochemical data of all 82 patients (and separately for grades I, II, and III) at the beginning and end of the study are summarized in Table 1. Serum TSH concentrations gradually increased in all groups, whereas fT_4 and T_3 levels remained constant. The two clinical scores [Billewicz (21) and Zulewski (16)] and ankle reflex time were well within the normal range throughout the study. Total, low density lipoprotein, and high density lipoprotein cholesterol and creatinine phosphate kinase also remained stable. These tests essentially excluded overt clinical and metabolic hypothyroidism (Table 1).

After a mean observation period of 9.2 yr, 23 of the 82 patients (28%) who entered the study with subclinical hypothyroidism developed overt hypothyroidism, as defined by low fT_4 and elevated TSH (>20 mU/liter). Fifty-six patients (68%) remained subclinically hypothyroid, and serum TSH returned to normal in 3 patients (4%, all from group I). According to the initial serum TSH concentrations (TSH, 4–6/>6–12/>12 mU/liter), Kaplan-Meier estimates of the incidence of overt hypothyroidism were 0%, 42.8%, and 76.9%, respectively, after 10 yr ($P < 0.0001$). When only patients with a serum TSH concentration above 6 mU/liter were analyzed (n = 61), the cumulative incidence of overt hypothyroidism was 55.3% after 10 yr. The mean annual rate of developing overt hypothyroidism in patients with TSH greater than 6 mU/liter was 5.6 ± 1.2%/yr (3.3 ± 1.5% for grade II and 11.4 ± 3.0% for grade III).

Of the 56 patients remaining subclinically hypothyroid, 17 (14%) were given thyroid hormone replacement therapy for clinical reasons other than overt hypothyroidism and were excluded from further follow-up. No patient developed hyperthyroidism during the observation period.

Patients with normal basal TSH levels but exaggerated TSH response after oral TRH stimulation and presenting minimal subclinical hypothyroidism were analyzed separately (grade 0; n = 29). No patient in this group developed overt hypothyroidism.

Prognostic factors for the development of overt hypothyroidism

Basal TSH. The spontaneous course of subclinical hypothyroidism for the entire cohort was further analyzed in relation to different biochemical prognostic factors. The incidence of overt hypothyroidism at the end of the study strongly correlated with the serum TSH level at initial evaluation (Fig. 1). The difference in the cumulative incidence among these three groups was highly significant (by log-rank test, $P < 0.0001$). In contrast, serum TSH became normal in three patients with grade I, but in none with grade II and III subclinical hypothyroidism.

Thyroid reserve (increase in T_3 after TRH). In subclinical hypothyroidism the thyroid reserve (T_3 increase after TRH) is dependent of the degree of thyroid failure [progressive impairment of thyroid reserve with increasing severity of hypothyroidism, as reported previously (4, 14, 19)]. At study entry the patients were divided into two groups: normal (>0.5 nmol/liter; n = 46) or impaired (≤0.5 nmol/liter; n = 36) thyroid reserve. The results demonstrate that thyroid reserve is an additional prognostic factor predicting which patients with subclinical hypothyroidism will develop overt hypothyroidism in the future ($P = 0.05$ after 10 yr; Fig. 1).

Antibody status. Antibody titers against microsomal antigen and thyroglobulin were classified as three degrees: 1) negative antibodies, 2) antibody titers 1–10 times above the normal range, and 3) antibody titers more than 10 times above the normal range. Antibodies against thyroglobulin did not have a predictive value for the development of thyroid failure. Patients with negative microsomal antibody titers (grade 1) had a significantly lower incidence of developing overt hypothyroidism than patients with positive (grades 2 and 3) titers (Fig. 1; $P = 0.03$).

Influence of radioiodine therapy

When all patients with radioiodine therapy (n = 32) were compared with all patients with autoimmune thyroiditis (n = 29), no significant difference was observed in the development of overt hypothyroidism ($P = 0.11$). When initial serum TSH concentrations in patients who further developed overt hypothyroidism were compared, no significant difference was observed (16.6 ± 2.9 *vs.* 15.3 ± 2.9 mU/liter; P = NS).

Smoking. Seventeen patients (20.7%) of the cohort were smokers, and 65 (79.3%) were nonsmokers. The incidence of overt hypothyroidism in these groups was not different (P = NS).

Cumulative prognostic value of different risk factors

After having analyzed the risk factors individually, we further examined their potential cumulative effect using the Cox proportional hazards model. TSH was the strongest risk factor for the development of overt thyroid failure. Analyzing all three prognostic factors, the calculated risk increased from 1.0 to 15.6 (Table 2).

Discussion

As there are limited data available describing the spontaneous course of subclinical hypothyroidism over a long time period, we studied a cohort of 82 patients with this syndrome in a prospective study at yearly intervals over a mean observation period of 9.2 yr, and we analyzed possible prognostic factors. This is, to our knowledge, the first systematic prospective study with annual controls over a prolonged time. During the observation period, clinical and biochemical evaluations were obtained annually to track the development of overt thyroid failure. It is generally believed that most, if not all, patients with subclinical hypothyroidism will eventually become hypothyroid. Our data demonstrate that after 10 yr 28% develop overt hypothyroidism over time, 68% remain in the subclinical stage, and a few (4%) become normal. However, the patients were only followed for about one third of their expected remaining lifetime. The rather small percentage of patients developing overt hypothyroidism is due in part to the fact that we also included some patients with mild forms of subclinical hypothyroidism (TSH, ≤6 mU/liter; n = 21). When patients with a serum TSH concentration of 6 mU/liter or less (grade I) were excluded, the cumulative incidence of overt hypothyroidism was 55.3% after 10 yr.

When analyzing subgroups presenting with different risk factors, major differences in outcome were observed. We thus analyzed the predictive value of basal serum TSH, thyroid reserve, and antibody status. Based on the initial serum TSH levels, patients with subclinical hypothyroidism were divided into three groups (*i.e.* grades I, II, and III). Kaplan-Meier estimates of the incidence of overt hypothyroidism in these groups were 0%, 42.8%, and 76.9%, respectively, after 10 yr. The calculated annual rate of developing overt hypothyroidism for patients with subclinical hypothyroidism (TSH >6 mU/liter) was 5.6 ± 1.2%/yr (3.3 ± 1.5% for grade II and 11.4 ± 3.0% for grade III). This is in agreement with the recent survey of a general population of healthy people with a reevaluation after 20 yr (Whickham study). They identified that serum TSH is an important risk factor for the development of overt hypothyroidism (22).

A classical approach in endocrinological investigation involves stimulation tests of target glands (*e.g.* ACTH for the adrenal gland, gonadotropins for the gonads, TSH for the thyroid). The thyroid can be stimulated by a rise in endogenous TSH induced by TRH or by the administration of recombinant human TSH (23). Thyroid reserve (T_3 increase after TRH) has been evaluated as a risk factor for developing overt hypothyroidism and has been shown to be decreased at an early stage of subclinical hypothyroidism (4, 14, 19). Thyroid reserve was inversely correlated with the development of overt hypothyroidism. The rise in T_3 after TRH administration shows a good correlation with basal TSH, as demonstrated previously (4, 14). The two parameters are affected in parallel by progressive thyroid failure. The degree of TSH elevation may reflect the thyroid damage and loss of function. The thyroid reserve contributes no additional risk factor for daily use, but it is a valuable research tool for the study of the functional capacity of the thyroid. For routine use the measurement of basal TSH alone is adequate.

The titer of thyroid antibodies correlates with lymphocytic infiltration of the thyroid, indicating autoimmune thyroid disease (24). In agreement with earlier reports (22, 25), the present data demonstrate that titers of microsomal antibodies are predictive of future thyroid failure. Antithyroglobulin antibodies were negative in most patients, and no prognostic value could be demonstrated. In our study positive microsomal antibodies contribute much less to the risk of developing overt hypothyroidism than basal TSH. This is at variance with the data from Vanderpump and colleagues (22), who found an identical risk for both tests. This could be explained in part by methodological factors (first generation TSH assay in 1972, and other methods for microsomal antibodies) and also by a different study population and selection (more autoimmune thyroiditis, fewer radioiodine-treated patients; epidemiological survey and no case-finding study).

We have reported that smoking increases serum TSH levels and the metabolic effects in patients with subclinical hypothyroidism in a dose-dependent way (19). However, in

TABLE 2. Calculated cumulative risk of the three risk factors TSH, microsomal antibodies (MAB), and thyroid reserve (ΔT3; Cox proportional hazards model)

	MAB negative		MAB positive		MAB 1–10 × above normal		MAB >10 × above normal	
	ΔT3 ≥ 0.5 nmol/liter	ΔT3 < 0.5 nmol/liter	ΔT3 ≥ 0.5 nmol/liter	ΔT3 < 0.5 nmol/liter	ΔT3 ≥ 0.5 nmol/liter	ΔT3 < 0.5 nmol/liter	ΔT3 ≥ 0.5 nmol/liter	ΔT3 < 0.5 nmol/liter
TSH ≤6 mU/liter	1	1.2	4.1	4.3	3.0	3.3	5.1	5.3
TSH >6–12 mU/liter	5.1	6.4	9.2	9.5	8.2	8.4	10.2	10.5
TSH >12 mU/liter	10.3	11.5	14.3	14.6	13.3	13.6	15.4	15.6

the present study smoking was not a risk factor for the later development of overt thyroid failure over time.

Using the Cox proportional hazards model we could demonstrate that basal serum TSH is the strongest predictive factor for overt hypothyroidism, followed by positive microsomal antibodies and impaired thyroid reserve: the relative risk increases by 15.6 in the highest risk group when all three of these parameters are present.

Our study demonstrates that initial grading is very important in predicting the outcome. Most patients with early subclinical hypothyroidism (grade I, TSH ≤6 mU/liter) may not require thyroid hormone therapy (no patient developed overt hypothyroidism after 9.2 yr). All patients with subclinical hypothyroidism grade III (TSH >12 mU/liter), however, should be treated with thyroid hormones. The risk for overt hypothyroidism in the group of patients with grade II dysfunction (TSH >6–12 mU/liter) can be assessed by measurements of microsomal or thyroperoxidase antibodies and thyroid reserve as prognostic factors. In addition to the risk for overt thyroid failure the clinical and metabolic manifestations of subclinical hypothyroidism must also be considered as indications for treatment. Despite normal levels of circulating thyroid hormones, some metabolic effects can be detected at the peripheral target tissues in individual patients with subclinical hypothyroidism (14, 26). In three former double-blind studies, positive effects on systolic time intervals and improvement of some hypothyroid symptoms and results of psychometric tests were described in some patients (27–29). Our group has recently shown in a double-blind study that physiological L-T_4 replacement in patients with subclinical hypothyroidism has a beneficial effect on low density lipoprotein cholesterol levels and clinical symptoms of hypothyroidism (30). Hence, the decision to treat patients with mild thyroid failure is dependent on the risk of developing overt hypothyroidism and the different clinical and metabolic conditions mentioned above.

In conclusion, our data clearly demonstrate that subclinical hypothyroidism has a variable outcome. In a cohort of female patients followed for more than 9.2 yr, three risk factors were predictive for overt thyroid failure: degree of TSH elevation, decreased thyroid reserve and the presence of microsomal (thyroperoxidase) antibodies. The initial risk stratification can identify patients with subclinical hypothyroidism at greatest risk for progression to overt hypothyroidism, mainly patients with TSH levels greater than 10 mU/liter, in which treatment with L-T_4 is mandatory. Our results support the actual guidelines in the latest review from Cooper, recently published in the *New England Journal of Medicine* (31).

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