0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 3
Printed in U.S.A.

Estimation of Tissue Hypothyroidism by a New Clinical Score: Evaluation of Patients with Various Grades of Hypothyroidism and Controls*

HENRYK ZULEWSKI, BEAT MÜLLER, PASCALE EXER, ANDRÉ R. MISEREZ, AND JEAN-JACQUES STAUB

Division of Endocrinology, Department of Medicine, University Hospital of Basel, Basel, Switzerland

ABSTRACT

The classical signs and symptoms of hypothyroidism were reevaluated in the light of the modern laboratory tests for thyroid function. We analyzed 332 female subjects: 50 overt hypothyroid patients, 93 with subclinical hypothyroidism (SCH), 67 hypothyroid patients treated with T_4, and 189 euthyroid subjects. The clinical score was defined as the sum of the 2 best discriminating signs and symptoms. Beside TSH and thyroid hormones, we measured parameters known to reflect tissue manifestations of hypothyroidism, such as ankle reflex relaxation time and total cholesterol.

Classical signs of hypothyroidism were present only in patients with severe overt hypothyroidism with low T_3, but were rare or absent in patients with normal T_3 but low free T_4 or in patients with SCH (normal thyroid hormones but elevated basal TSH; mean scores, 7.8 ± 2.7 *vs.* 4.4 ± 2.2 *vs.* 3.4 ± 2.0; $P < 0.001$). Assessment of euthyroid subjects and T_4-treated patients revealed very similar results (mean score, 1.6 ± 1.6 *vs.* 2.1 ± 1.5). In overt hypothyroid patients, the new score showed an excellent correlation with ankle reflex relaxation time and total cholesterol ($r = 0.76$ and $r = 0.60$; $P < 0.0001$), but no correlation with TSH ($r = 0.01$). The correlation with free T_4 was $r = -0.52$ ($P < 0.0004$), and that with T_3 was $r = -0.56$ ($P < 0.0001$). In SCH, the best correlation was found between the new score and free T_4 ($r = -0.41$; $P < 0.0001$) and TSH ($r = 0.35$; $P < 0.0005$).

Evaluation of symptoms and signs of hypothyroidism with the new score in addition to thyroid function testing is very useful for the individual assessment of thyroid failure and the monitoring of treatment. (*J Clin Endocrinol Metab* **82:** 771–776, 1997)

THE DEVELOPMENT of highly sensitive and precise methods for the measurement of total and free thyroid hormones and, mainly, TSH makes the diagnosis of obvious thyroid dysfunction easy. However, using these methods, more and more atypical laboratory constellations can be found, including subclinical forms of hypothyroidism and hyperthyroidism (1–6), as well as various other conditions, such as resistance to thyroid hormones (7), and many divergent laboratory results due to drugs interfering with hormone metabolism or determination (8).

In these cases, and especially in subclinical hypothyroidism, the decision to treat is often determined by the physician's assessment of the clinical severity of the disease (2, 3). Therefore, it would be useful to have a symptom-rating scale to assess the clinical status and the potential effect of treatment. Three decades ago in 1969 Billewicz *et al.* (9) described a diagnostic index that scores the presence or absence of various signs and symptoms of hypothyroidism for the purpose of establishing a diagnosis. However, modern thyroid function tests were not available at the time of their studies.

The aim of our study was to reevaluate the signs and symptoms of hypothyroidism in the light of modern thyroid function tests and to develop a new convenient clinical score for individual assessment of the severity of thyroid failure. Additionally, we tested the ability of the clinical score to reflect tissue hypothyroidism by correlation analyses with TSH, thyroid hormones, and some tests reflecting thyroid hormone action at target tissues, such as ankle reflex time (ART) and total cholesterol (TC) levels (6).

Subjects and Methods

Patients and controls

The 332 study subjects were selected from a cohort of patients and normal controls studied in a prospective manner in the Endocrine Outpatient Clinic of the University Hospital of Basel as a part of a project of the Swiss Research Foundation on hypothyroidism (6). The study was approved by the ethics committee for human studies of the University of Basel, and informed consent was given by each subject. Only females were included so as to exclude variations due to sex. All hypothyroid patients were ambulatory and in good general health. All euthyroid subjects were normal women; mainly staff members, their relatives, and friends. After an overnight fast, all the women underwent full medical assessment and laboratory examinations (hematology and blood chemistry and urine analysis) to exclude nonthyroidal illness.

Derivation sample

To define the new clinical score, we analyzed 50 patients (aged 55.2 ± 13.1 yr) with overt primary hypothyroidism characterized by elevated basal TSH (>20 mu/L) and decreased free T_4 (fT_4; <8 pmol/L) and 80 age-matched female euthyroid controls (aged 51.6 ± 9.9 yr). All controls underwent a euthyroid test with oral TRH (10). The underlying thyroid disorders were autoimmune thyroiditis (n = 30), treated Graves' disease (n = 18), thyroidectomy for simple goiter (n = 1), and treated toxic adenoma (n = 1).

Received August 13, 1996. Revision received October 28, 1996. Accepted November 20, 1996.

Address all correspondence and requests for reprints to: Jean-Jacques Staub, M.D., Division of Endocrinology, Department of Medicine, University Hospital of Basel, CH-4031 Basel, Switzerland.

* This work was supported by grants from the Swiss Research Foundation (3.907–0.88/32.27866.-89), the Sandoz Research Fund, and Henning Berlin.

Definition of the new clinical score

Fourteen symptoms and signs of hypothyroidism (Fig. 1) were evaluated by various physicians in our endocrine clinic in all patients and controls as described by Billewicz *et al.* (9). The physicians did not know the laboratory data of the patients and control subjects, which were available after the clinical examination only. The frequencies of symptoms and signs were calculated as well as their sensitivity, specificity, and positive and negative predictive values. They were quantified by a simple and convenient system: 1 point = present, and 0 points = absent. The value of the total score is given as the sum of the symptoms and signs present (Tables 1 and 2).

Validation of the new clinical score

In a second phase of the study the new clinical score was assessed in 93 patients with subclinical hypothyroidism (SCH; aged 52.7 ± 12.7 yr) defined by elevated basal TSH (above 4 mU/L) and fT_4 and T_3 values within the respective reference ranges. The etiology of thyroid failure was treated Graves disease in 44 women, autoimmune thyroiditis in 35, thyroidectomy for simple goiter in 13 women, and treated toxic adenoma in 1 woman. In addition, we analyzed 109 euthyroid women with normal basal TSH and normal fT_4 values (aged 43.4 ± 14.7 yr) as well as 67 of the 143 hypothyroid patients (aged 56.3 ± 13.3 yr; 28 with subclinical and 39 with overt hypothyroidism) when they were euthyroid after treatment with T_4 for at least 3 months, as confirmed by a normal TSH response to oral TRH (10) on 2 separate occasions (mean T_4 dose, 103 ± 27.5 μg/day).

Hormone measurements and tests of peripheral hormone action

TSH (normal, 0.1–4.0 mU/L; assay sensitivity, 0.10 mU/L) was determined by an immunoradiometric assay [h-TSH Behring (RIA-gnost), Frankfurt, Germany]. Before introduction of this second generation TSH assay, we used a conventional RIA for TSH determinations. The correlation analysis showed an excellent correlation between these two methods (n = 94; r = 0.926; $P < 0.0001$). fT_4 (normal, 8.0–27 pmol/L) and T_3 (0.9–3.0 nmol/L) were measured by RIA (10, 11). ART was assessed as a mean of six readings by photomotogram with an achillometer (Polymed A.G., Glattbrugg, Switzerland) recording three tracings on each side (normal range, 280–420 ms) (6). Creatine kinase (CK; normal range, 40–160 U/L), TC, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were measured by standard methods as described previously (6).

Statistical analysis

All data are expressed as the mean ± SD. Differences between mean values of variables were tested by one-way ANOVA, and differences between frequencies were determined by the χ^2 test. To assess the relationship between the new clinical score and other parameters, a nonparametric regression model (Spearman) was used. Receiver operating characteristic curves were generated for direct comparison (independent of the chosen cut-off points) of the new score with the Billewicz index (Fig. 2).

Results

Hormone measurements

The mean values of TSH, fT_4, and T_3 are summarized in Table 3.

Clinical analysis of and definition of the new clinical score

The frequencies of the 14 symptoms and signs in the derivation sample are shown in Fig. 1. Most frequent in the hypothyroid patients were prolonged ART (77%) and complaints about dry skin (76%). Some symptoms were also observed with a high frequency in euthyroid controls. Pulse rate and cold intolerance had positive and negative predictive values below 70% (Table 1) and were, therefore, excluded from the new score.

In the control group, older women (≥55 yr; n = 31) presented more often with hypothyroid symptoms, especially constipation ($P < 0.005$) and dry skin ($P < 0.05$), compared

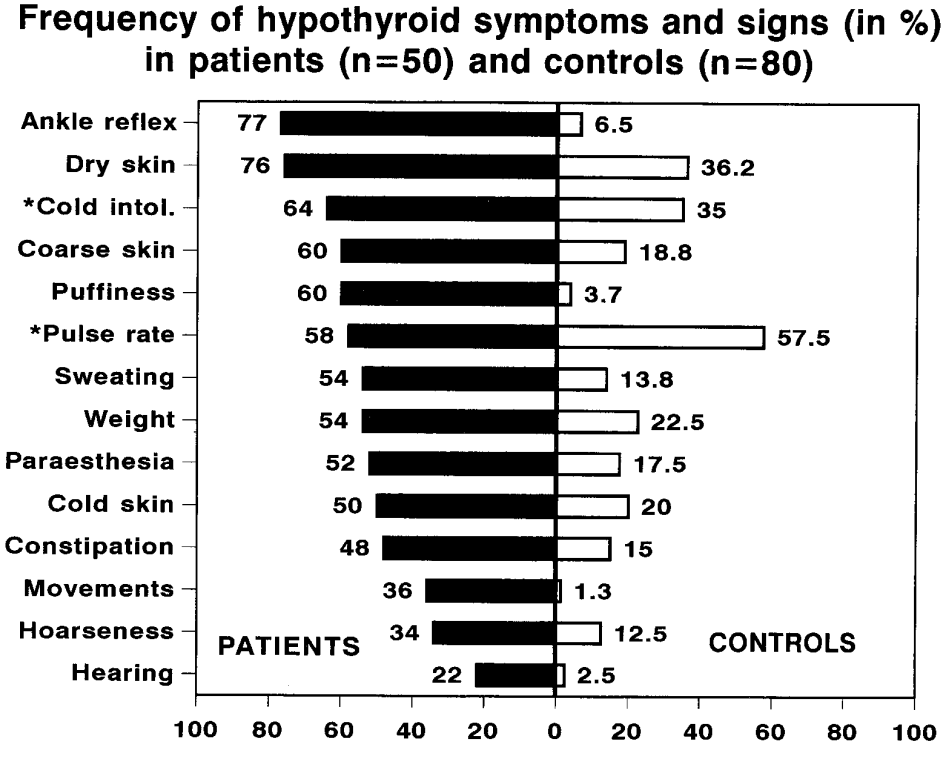

FIG. 1. Frequency of hypothyroid symptoms and signs (percentage) in 50 patients with overt hypothyroidism and 80 euthyroid controls. Two symptoms (pulse rate and cold intolerance) showed positive and negative predictive values of less than 70% and were, therefore, excluded from the new score.

TABLE 1. Sensitivity and specificity of the 14 symptoms and signs of hypothyroidism and analysis of their positive and negative predictive values

Symptoms and signs	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Ankle reflex	77	93.5	92.2	80.3
Dry skin	76	63.8	67.7	72.7
Cold intolerance[a]	64	65	64.6	64.4
Coarse skin	60	81.2	76.1	67
Puffiness	60	96.3	94.2	70.7
Pulse rate[a]	58	42.5	50.2	50.3
Sweating	54	86.2	79.6	65.2
Wt increase	54	77.5	70.6	62.8
Paraesthesia	52	82.5	74.8	63.2
Cold skin	50	80	71.4	61.5
Constipation	48	85	76.2	62
Slow movements	36	98.7	96.5	60.7
Hoarseness	34	87.5	73.1	57
Hearing	22	97.5	89.8	52.6

[a] Two signs (cold intolerance and decreased pulse rate) showed positive and negative predictive values below 70% and were, therefore, excluded from the new score.

TABLE 2. Scoring of symptoms and signs of hypothyroidism

	On the basis of	New score	
		Present	Absent
Symptoms			
Diminished sweating	Sweating in the warm room or a hot summer day	1	0
Hoarseness	Speaking voice, singing voice	1	0
Paraesthesia	Subjective sensation	1	0
Dry skin	Dryness of skin, noticed spontaneously, requiring treatment	1	0
Constipation	Bowel habit, use of laxative	1	0
Impairment of hearing	Progressive impairment of hearing	1	0
Wt increase	Recorded weight increase, tightness of clothes	1	0
Physical signs			
Slow movements	Observe patient removing his clothes	1	0
Delayed ankle reflex	Observe the relaxation of the reflex	1	0
Coarse skin	Examine hands, forearms, elbows for roughness and thickening of skin	1	0
Periorbital puffiness	This should obscure the curve of the malar bone	1	0
Cold skin	Compare temperature of hands with examiner's	1	0
Sum of all symptoms and signs present		12	0

For clinical judgment, add 1 point to the sum of symptoms and signs present in women younger than 55 yr.
Hypothyroid, more than 5 points; euthyroid, less than 3 points; intermediate, 3–5 points.

with younger controls (<55 yr; n = 49). The new score was considerably higher in older women (2.3 ± 1.5 *vs.* 1.2 ± 1.2; $P < 0.001$). The correlation analysis revealed a significant correlation of the new score with age (r = 0.40; $P < 0.0004$). For the clinical judgment of hypothyroidism, we, therefore, defined a simple age-correcting factor by adding 1 point to the sum of symptoms and signs in women younger than 55 yr.

The diagnostic ranges for the new score were set to achieve positive and negative predictive values of more than 90% for the clinical diagnosis or exclusion of hypothyroidism. This was obtained by choosing two cut-off points: hypothyroid range, more than 5 points (positive predictive value, 96.9%); euthyroid, 2 points or less (negative predictive value for exclusion of hypothyroidism, 94.2%); and intermediate range, 2–5 points. The values for sensitivity and specificity were 62% and 99% for the cut-off points 5% and 94%, respectively, and 61% for the cut-off point 2. According to this analysis, the following diagnostic ranges for the clinical judgment with the new (age corrected) score were defined: hypothyroid, more than 5 points; euthyroid, 0–2; and intermediate range, 3–5 points.

Using this definition, 62% of all overt hypothyroid patients were classified as clinically hypothyroid by the new score [42% using the definition of Billewicz *et al.* (9)]. In the subgroup of patients with diminished T_3, 84% were assessed as clinically hypothyroid (Billewicz index, 76%), whereas 40% of the patients with normal T_3 reached the hypothyroid range (Billewicz index, 8%). Surprisingly, we found two patients who were clinically euthyroid with both scoring methods despite marked biochemical hypothyroidism (basal TSH, 63.6 and 42.3 mU/L; fT_4, 3.2 and 3.9 pmol/L, respectively, with normal T_3 in one and low T_3 in the other patient). 61% of the euthyroid controls were assessed as clinically euthyroid by the new score (Billewicz index, 52%), and one control subject was in the hypothyroid range (none with a Billewicz index value). The remaining controls were classified into the intermediate range (new score, 38%; Billewicz index, 48%; Fig. 3).

Validation of the new clinical score

Of the subclinically hypothyroid patients (n = 93), 24% (Billewicz index, 6%) were designated hypothyroid, 29% (Billewicz index, 29%) were designated euthyroid, and

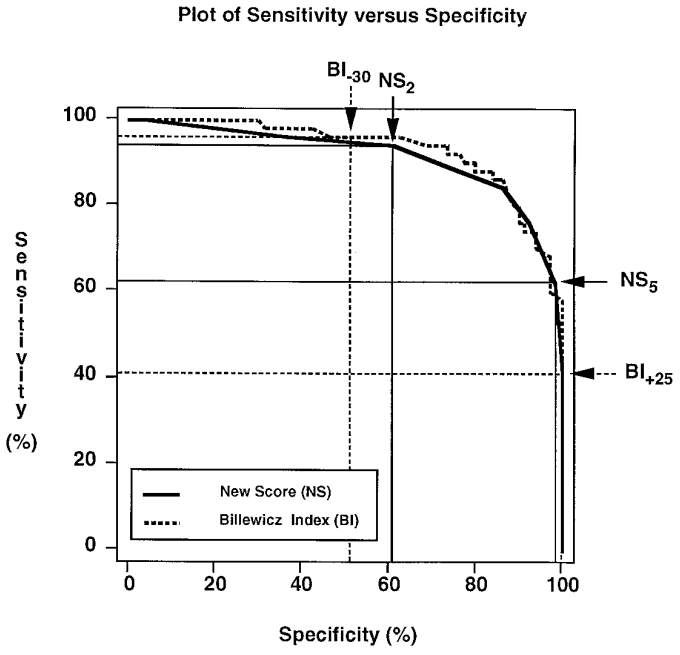

FIG. 2. Receiver operating characteristic curves, describing the relationship of sensitivity and specificity for the new score and the Billewicz index in the total study group. The cut-off points for clinical diagnosis or exclusion of hypothyroidism with the new score (5 points = NS_5 and 2 points = NS_2) and the Billewicz index (BI_{+25} and BI_{-30}) are marked by *arrows*.

47% (Billewicz index 65%) were scored in the intermediate range. The corresponding values for the second group of euthyroid subjects (n = 109) are (Billewicz index in *parentheses*): euthyroid, 66% (67%); hypothyroid, 6% (0%); and intermediate range, 28% (33%). Of the T_4-treated patients (n = 67), 55% (52%) were in the euthyroid range, 2% (0%) were assessed as hypothyroid, and 43% (48%) were classified in the intermediate range.

Possible effect of smoking

Smoking has been shown recently to aggravate the clinical and metabolic expression of hypothyroidism (12). We, therefore, analyzed the new score in smokers and nonsmokers in all study subjects. The percentage of smokers in our study population was 19.5%. In euthyroid subjects, smoking did not affect the clinical evaluation. The new scores in all euthyroid women (n = 189) and T_4-treated patients were: smokers *vs.* nonsmokers, 1.6 ± 1.7 *vs.* 1.6 ± 1.4 and 2.2 ± 1.5 *vs.* 2.1 ± 1.5 (P = NS for both comparisons). In SCH, the clinical score was slightly higher in smokers (3.8 ± 2.1 *vs.* 3.2 ± 1.9; P = NS). In overt hypothyroidism, however, smokers presented with a significantly higher clinical score than nonsmokers (7.6 ± 3.2 *vs.* 5.5 ± 2.7; $P = 0.024$).

Other tests of peripheral hormone action

The body mass index (BMI) was increased in overt hypothyroid patients compared to that in controls ($P < 0.01$). The BMI was clearly elevated in the subgroup of patients with severe hypothyroidism ($P < 0.001$) and was moderately elevated in patients with overt hypothyroidism but normal T_3 (Table 3). Interestingly, the patients with SCH had a significantly higher BMI than the age-matched controls ($P < 0.01$).

The TC and LDL-C values were elevated in the group of all overt hypothyroid patients ($P < 0.001$) combined with a decrease in HDL-C ($P < 0.05$). This was primarily due to the marked changes in the subgroup of patients with decreased T_3 ($P < 0.001$), whereas in patients with normal T_3, these parameters were only slightly altered compared with those in the controls (P = NS; Table 3). In SCH, the TC and LDL-C values were very similar to the control values. The HDL-C was slightly decreased ($P < 0.05$).

The values for ART and CK were clearly elevated in overt hypothyroidism in both subgroups with normal and decreased T_3 ($P < 0.001$; Table 3). In SCH, the ART was also increased ($P < 0.001$) compared with that in the age-matched controls, whereas CK was not.

Correlation of the new clinical score with the laboratory findings

In the group of overt hypothyroid patients the new score showed an excellent correlation with tests of peripheral hormone action: for ART, r = 0.76; $P < 0.0001$; for TC, r = 0.60; $P < 0.0001$; and for CK, r = 0.55; $P < 0.0003$. However, no correlation was found with TSH (r = 0.01; P = NS). The correlation of the new score with thyroid hormones was similar or weaker compared with tests of peripheral hormone action: for fT_4, r = −0.52; $P < 0.0004$; and for T_3, r = −0.56; $P < 0.0001$. To avoid a possible bias due to comparison of measured ART with the clinical sign of delayed ankle reflex included in the score, we repeated the correlation analysis of the new score after removal of this clinical sign. Nevertheless, a similar result was obtained (r = 0.71; $P < 0.0001$). In contrast to overt hypothyroidism, in SCH the best correlation was found between the new score and fT_4 (r = −0.41; $P < 0.0001$) and TSH (r = 0.35; $P < 0.0005$). The correlations of the new score with metabolic parameters of hypothyroidism were preserved in SCH: for ART, r = 0.33; $P < 0.001$; and for TC, r = 0.28; $P < 0.01$.

Discussion

The results of the present study demonstrate that the modern laboratory tests for thyroid function have completely changed the clinical picture of hypothyroidism. This is the first study for 3 decades that reevaluated systematically the symptoms and signs of hypothyroidism. According to our data, the prevalence of the typical hypothyroid symptoms in overt hypothyroidism is remarkably different from that described in the classical, but also in recent, literature (13). The classical symptoms and signs (*e.g.* coarse skin, cold intolerance, decreased sweating, or puffiness) are still described as having a high frequency of 90–97%, but they were observed much less often in our patients (50–64%). In most textbooks the results of old investigations are included, which were performed several decades ago, at a time when measurements of thyroid hormones and TSH were not available. It is likely that only patients with severe and long standing hypothyroidism were diagnosed at that time.

Some symptoms of hypothyroidism may also be common in euthyroid individuals. In our age-matched euthyroid con-

TABLE 3. Data of patients and controls

Parameter	Derivation sample				Validation sample		
	Controls (n = 80)	Overt Hypothyroidism			Subclinical hypothyroidism (n = 93)	T_4 Therapy (n = 67)	New euthyroid subjects (n = 109)
		Normal T_3 (n = 25)	Low T_3 (n = 25)	All patients (n = 50)			
TSH (mU/L)	1.6 ± 0.77	46.0 ± 22.9[a]	52.3 ± 23.3[a]	49.2 ± 23.1[a]	13.7 ± 10.6[a]	1.9 ± 1.50	1.5 ± 0.76
fT4 (pmol/L)	16.5 ± 3.53	5.0 ± 1.90[a]	3.3 ± 1.35[a]	4.2 ± 1.84[a]	12.5 ± 2.83[a]	18.7 ± 3.86	15.6 ± 3.38
T_3 (nmol/L)	1.9 ± 0.62	1.2 ± 0.34[a]	0.7 ± 0.16[a]	0.96 ± 0.39[a]	1.8 ± 0.37[b]	1.6 ± 0.40	1.9 ± 0.51
BMI (kg/m^2)	23.5 ± 3.5	23.3 ± 3.1[c]	27.2 ± 3.2[a]	25.2 ± 3.7[d]	25.3 ± 4.3[d]	25.3 ± 3.8	23.2 ± 3.5
TC (mmol/L)	6.38 ± 1.11	6.68 ± 1.49[c]	9.33 ± 2.10[a]	8.0 ± 2.24[a]	6.32 ± 1.42[c]	6.20 ± 1.06	5.68 ± 1.44
LDL-C (mmol/L)	4.02 ± 1.02	4.56 ± 1.58[c]	6.56 ± 1.72[a]	5.5 ± 1.92[a]	4.23 ± 1.37[c]	4.14 ± 1.01	3.60 ± 1.29
HDL-C (mmol/L)	1.53 ± 0.26	1.46 ± 0.19[c]	1.36 ± 0.23[a]	1.4 ± 0.22[b]	1.41 ± 0.30[b]	1.34 ± 0.20	1.50 ± 0.26
ART (ms)	350 ± 36	420 ± 113[a]	555 ± 104[a]	495 ± 126[a]	385 ± 43[a]	384 ± 42	355 ± 39
CK (U/L)	84.1 ± 35.0	193 ± 164[a]	587 ± 844[a]	390 ± 633[a]	87.5 ± 42.7[c]	87.2 ± 42.1	84.5 ± 38.7
Billewicz index	−31 ± 14.3	0 ± 23.5[a]	36 ± 26.2[a]	18 ± 30.8[a]	−15 ± 23.0[a]	−27 ± 16.7	−34 ± 15.6
New score	1.6 ± 1.4	4.4 ± 2.2[a]	7.8 ± 2.7[a]	6.1 ± 3.0[a]	3.4 ± 2.0[a]	2.1 ± 1.5	1.6 ± 1.6

Significance was determined by ANOVA: patients with overt and subclinical hypothyroidism *vs.* age matched controls. Values are the mean ± SD.

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] P = NS.
[d] $P < 0.01$.

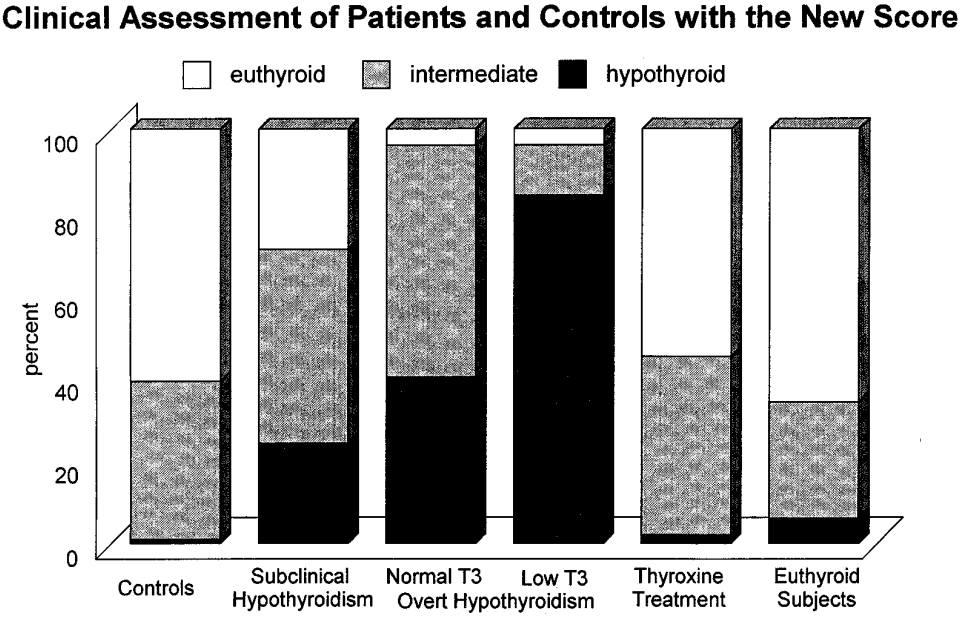

FIG. 3. Clinical assessment of patients and controls with the new clinical score in overt hypothyroidism (n = 50), age-matched controls (n = 80), subclinical hypothyroidism (n = 93), hypothyroid patients treated with T_4 (n = 67), and an additional sample of euthyroid subjects (n = 109).

trols these symptoms were more frequent in older females (55 yr), which resulted in higher values for the new clinical score than those in younger controls (2.3 1.5 *vs.* 1.2 1.2; $P <$ 0.001). Therefore, we defined a convenient age-correcting factor (*i.e.* addition of 1 point to the sum of positive symptoms and signs in subjects younger than 55 yr) for clinical assessment.

Using this definition, 62% of all overt hypothyroid and 24% of subclinical hypothyroid patients could be classified as clinically hypothyroid by the new score, 42% and 6% using the definition of the Billewicz index. This result may suggest a diagnostic superiority of the new score compared to the Billewicz index. However, the characteristics of the receiver operating curves reflecting the relationship between sensitivity and specificity are very similar for both scoring methods, as illustrated in Fig. 2. Compared with the Billewicz index, the main advantage of the new score is its convenient and simple scoring system.

In the age-matched control group (n = 80), 61% were classified as clinically euthyroid by the new score. A similar proportion of T_4-treated patients and the second sample of euthyroid subjects were also assessed as euthyroid (55% and 66%), showing the good reproducibility of the clinical evaluation in euthyroid subjects with the new score.

Recently, smoking was described to aggravate clinical and metabolic manifestations of thyroid failure (12). In the present study we also found a tendency toward higher values for the new score in smokers compared to nonsmokers with SCH (3.8 ± 2.1 *vs.* 3.2 ± 1.9; P = NS) and significantly elevated values in smokers with overt hypothyroidism (7.6 ±

3.2 *vs.* 5.5 ± 2.7; $P = 0.024$) in contrast to no effect of smoking on the clinical score in euthyroid women or T_4-treated patients.

It is of special interest that some patients with severe biochemical hypothyroidism had only mild clinical signs, whereas other patients with minor biochemical changes had quite severe clinical manifestations. Thus, we assume that tissue hypothyroidism at the peripheral target organs must be different in the individual patient. Therefore, the clinical score can give a valuable estimate of the individual severity of metabolic hypothyroidism. In overt hypothyroidism we could demonstrate that the new score correlates as well as or even better with parameters reflecting tissue hypothyroidism, such as ART and TC, than with circulating thyroid hormones or TSH. Using the nonparametric regression model, we found a very good correlation for ART but no correlation for TSH, despite the fact that the pituitary is also a target organ for thyroid hormones. In SCH, the early stage of thyroid failure, however, the best correlation was present between the new score and fT_4 and basal TSH. There is no doubt that basal TSH is the best parameter for early detection of thyroid dysfunction. In overt hypothyroidism, however, the pituitary TSH stimulation is probably at the top of the dose-response curve with maximal TSH secretion, and therefore, basal TSH becomes a poor indicator of tissue hypothyroidism in advanced thyroid failure. Discordant responses between the pituitary and peripheral target tissues have been described in patients with primary hypothyroidism treated with L-T_3 (14).

Faced with the variability of the clinical findings in overt and subclinical hypothyroidism, we cannot recommend the use of the new clinical score for the purpose of establishing the diagnosis of hypothyroidism. Routine thyroid function testing is the best and most reliable way to identify patients with thyroid failure. The purpose of this score is to assess the severity of tissue hypothyroidism, to evaluate patients with discordant laboratory results, and to monitor the effect of treatment, especially in subclinical hypothyroidism. As in our T_4-treated group of patients, one of the major findings of Cooper and colleagues (15) and Nystrom and colleagues (16) in assessing patients with SCH treated with T_4 was that their patients felt better when treated, even if they did not feel badly initially. Therefore, clinical evaluation using a standardized score can give valuable information about the individual severity of impaired thyroid function and the effect of treatment. According to a recent statement: "The ultimate test of whether a patient is experiencing the effects of too much or to little thyroid hormone is not the measurement of hormone concentration in the blood but the effect of thyroid hormones on the peripheral tissues" (17).

Acknowledgments

We express our gratitude to the many physicians who referred the patients for this study. We thank Prof. G. Brabant (Hannover, Germany) and Dr. A. Ryff (Basel) for their useful criticism in reviewing the manuscript. The measurements of TSH and thyroid hormones were performed at the Hormone Laboratory (PD Dr. P. Huber), Department of Chemical Pathology, and the lipid analyses were conducted at the Lipid Laboratory (Prof. U. Keller) of the University Hospital of Basel.

References

1. **Anonymous** 1986 Subclinical hypothyroidism [Editorial]. Lancet. 1:251–252.
2. **Drinka PJ, Nolten WE.** 1988 Subclinical hypothyroidism in the elderly: to treat or not to treat. Am J Med Sci. 295:125–128.
3. **Cooper DS.** 1991 Subclinical hypothyroidism. In: Mazzaferri EL, ed. Advances in endocrinology and metabolism. St. Louis, Baltimore, Boston: Mosby-Year Book; vol 2:77–88.
4. **Gemsenjäger E, Staub JJ, Girard J, Heitz PH.** 1976 Preclinical hyperthyroidism in multinodular goiter. J Clin Endocrinol Metab. 43:810–816.
5. **Ross DS.** 1991 Subclinical thyrotoxicosis. In: Mazzaferri EL, ed. Advances in endocrinology and metabolism. St. Louis, Baltimore, Boston: Mosby-Year Book; vol 2:89–105.
6. **Staub JJ, Althaus BU, Engler H, et al.** 1992 The spectrum of subclinical and overt hypothyroidism: effect on TSH, prolactin, thyroid reserve and metabolic impact on target tissues. Am J Med. 92:631–642.
7. **Refetoff S.** 1982 Syndromes of thyroid hormone resistance. Am J Physiol. 243:E88–E98.
8. **Davies PH, Franklyn JA.** 1991 The effect of drugs on tests of thyroid function. Eur J Clin Pharmacol. 40:439–451.
9. **Billewicz WZ, Chapman RS, Crooks J, et al.** 1969 Statistical methods applied to the diagnosis of hypothyroidism. Q J Med. 38:255–266.
10. **Staub JJ, Noelpp B, Gräni R, Gemsenjäger E, Hauenstein M, Girard J.** 1983 The relationship of serum thyrotropin (TSH) to the thyroid hormones after oral TSH-releasing hormone in patients with preclinical hypothyroidism. J Clin Endocrinol Metab. 56:449–453.
11. **Staub JJ, Ryff-de Lèche AS, Paul S, Girard J, Polc B, von der Ohe M.** 1985 Intranasal thyrotrophin releasing hormone is a potent stimulus for TSH release in man (comparison with intravenous and oral TRH). Clin Endocrinol (Oxf). 22:567–572.
12. **Müller B, Zulewski H, Huber P, Ratcliffe JG, Staub JJ.** 1995 Impaired thyroid hormone action associated with smoking in women with hypothyroidism. N Engl J Med. 333:964–969.
13. **Larsen PR, Ingbar SH.** 1992 The thyroid gland. In Wilson JD, Foster DW, eds. Williams textbook of endocrinology, 8th ed. Philadelphia: Saunders; 357–487.
14. **Ridgway EC, Cooper DS, Walker H, et al.** 1980 Therapy of primary hypothyroidism with L-triiodothyronine: discordant cardiac and pituitary responses. Clin Endocrinol (Oxf). 13:479–488.
15. **Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC.** 1984 L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. Ann Intern Med. 101:18–24.
16. **Nyström E, Caidahl K, Fager G, Wikkelsö C, Lundberg P-A, Lindstedt G.** 1988 A double-blind cross-over 12-month study of L-thyroxine treatment of women with "subclinical" hypothyroidism. Clin Endocrinol (Oxf). 29:63–76.
17. **Greenspan FS, Rapoport B.** 1991 Tests of thyroid function. In: Greenspan FS, ed. Basic and clinical endocrinology, 3rd ed. London: Appleton & Lange, Prentice Hall International; 211.