Incidence of Thyroid Disorders in Systemic Sclerosis: results from a longitudinal follow-up.

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Abstract

Context: Systemic sclerosis (SSc) is a connective tissue disease of unknown aetiology and several studies reported its association with thyroid autoimmune disorders. No study has evaluated longitudinally the incidence of new cases of thyroid autoimmunity and dysfunction in SSc patients.

Objective: To evaluate the incidence of new cases of clinical and subclinical thyroid dysfunction in a wide group of women with SSc, versus an age- and gender-matched control group from the same geographic area.

Design and Patients or Other Participants: After exclusion of sclerodermic patients with thyroid dysfunction (n=55) at the initial evaluation, the appearance of new cases of thyroid disorders was evaluated in 179 patients and 179 matched controls, with similar iodine intake (median follow-up 73 months in SSc versus 94 in controls).

Results: A high incidence ($P < 0.05$) of new cases of hypothyroidism, thyroid dysfunction, anti–thyroperoxidase antibody positivity, appearance of a hypoechoic thyroid pattern in sclerodermic patients (15.5, 21, 11, 14.6/1000 patients per year; respectively) versus controls was shown. A logistic regression analysis showed that in SSc patients the appearance of hypothyroidism was related to a border line high initial thyroid stimulating hormone, anti–thyroperoxidase antibody positivity, a hypoechoic and small thyroid.

Conclusions: Our study shows a high incidence of new cases of hypothyroidism and thyroid dysfunction in female sclerodermic patients. Female sclerodermic patients, who are at high risk [a border line high (even if in the normal range) thyroid stimulating hormone, positive anti–thyroperoxidase antibody, hypoechoic and small thyroid] should have periodically thyroid function follow-up.

Introduction

Discordant results on the association between thyroid autoimmunity and Systemic sclerosis (SSc) have been reported (1-5). However, no study has evaluated longitudinally the incidence of new cases of thyroid autoimmunity and dysfunction in SSc patients.

The aim of our study was to evaluate the incidence of new cases of clinical and subclinical thyroid dysfunction in a wide group of SSc women.

Patients and Methods

Two hundred and thirty-four female SSc patients (6,7) consecutively referred to the Rheumatology Units of the University of Pisa and Modena (from 1993 to 2008) underwent a thyroid evaluation (7).

Among the 234 SSc patients, those with subclinical or clinical hypothyroidism, subclinical hyperthyroidism or Graves' disesase, were excluded. One hundred seventy-nine SSc patients without thyroid dysfunction were eligible for the longitudinal study (43 from Modena). They were studied again, at least 1 year after the initial evaluation, one or more times. The mean follow-up period from the initial evaluation was 68 months (range 12-175 months, median 73 months).

Skin sclerosis was observed in all patients (diffuse 43, or limited 57%; visceral involvement included: peripheral vascular system, 93%; gastrointestinal system, 55%; lung, 64%; joint/tendons, 24%; heart, 27%; kidney, 13%). The prevalence of autoantibodies (2,3) was: antinuclear 92%, anticentromere 35%, anti-topoisomerase I (anti-Scl-70) 44%.

Each of the 179 female SSc patients eligible for the study was gender- and age-matched, one-to-one with a control group, without thyroid dysfunction, of the background population from the same geographic area (North-West Tuscany) (8). This control group was extracted from a larger sample of 1081 subjects in a population-based survey of thyroid disorders, who were initially studied in 1994 and subsequently reevaluated (by thyroid function, autoantibodies and ultrasonography) in 2002-2003 (see above).

Since thyroid autoimmunity is affected by iodine intake (9), morning urinary samples were collected from 97 SSc patients and 108 controls. Urinary iodine excretion (UIE) was measured by a

colorimetric method (10). The results were calculated as micrograms of iodine per liter of urine and are expressed as median and interquartile range (IR).

The mean follow-up period from the initial evaluation was 95 months (range 87-106 months, median 94 months). All SSc patients and controls were reevaluated, by: a- physical examination; b- thyroid ultrasonography, as previously reported (11); c- thyroid nodules with a diameter > 10 mm were submitted to ultrasonography-guided fine-needle aspiration (FNA) (11); d- circulating free T3 (FT3) and free T4 (FT4) (AMERLEX-MAB FT3/FT4 Kit; Amersham, UK), TSH (reference range 0.3-3.6 μU/mL) (DiaSorin, USA), anti–thyroperoxidase (AbTPO) and anti–thyroglobulin (AbTg) antibodies (ICN Pharmaceuticals, USA; positivity > 100 IU/mL). Anti-TSH-receptor antibodies (TRAb) were measured in patients with hyperthyroidism (Radim, Italy; normal range 0-1 IU/mL).

If thyroid dysfunction appeared during the follow-up, SSc patients were appropriately treated and excluded from a further evaluation.

The study was approved by the institutional ethic committee, and all subjects gave their informed written consent to participate.

Mean group values were compared using one-way ANOVA for normally distributed variables, otherwise by the Mann-Whitney U test. The χ^2 test was used to compare categorical variables. A logistic regression analysis was performed including age, smoking, TSH, AbTPO positivity, AbTg positivity, thyroid hypoechogenicity (presence/absence), thyroid volume (all at the start of evaluation) as independent variables, and hypothyroidism at last evaluation as dependent variable.

Results

Longitudinal study

After the exclusion of patients with thyroid dysfunction and thyroid cancer (55 patients), the thyroid status of SSc patients entering the longitudinal study and matched controls is reported in **Table 1**.

UIE in SSc patients and in controls was not significantly different (median 87.0 μg/L, IR 39.0–143.5 μg/L; median 79.0 μg/L, IR 34.3–138.6 μg/L, respectively; *P* = ns).

The prevalence of subjects with positive AbTPO, thyroid hypoechoic pattern, and thyroid volume < 6 mL were significantly higher in the SSc group than in controls (**Table 1**), while TSH was slightly but significantly higher in SSc patients. On the whole, indices of thyroid autoimmunity (AbTg, or AbTPO, or ultrasonographic diagnosis of thyroiditis) were significantly more frequent in SSc than in controls. No other statistically significant difference was observed at basal evaluation.

At the last evaluation (after a median of 73 and 94 months, respectively in SSc and controls: $P < 0.01$, ANOVA) TSH levels and AbTPO titers were significantly higher in SSc than in controls (**Table 1**). Subclinical hypothyroidism was significantly more common in SSc than in controls, while clinical hypothyroidism did not reach the significance. Two cases of Graves' disease were observed in SSc patients, while no case was observed in controls. The prevalence of subclinical hyperthyroidism was similar in SSc and controls. On the whole the prevalence of thyroid dysfunction (subclinical or clinical hypo- and hyper-thyroidism) was significantly more frequent in SSc patients (**Table 1**). The prevalence of subjects with positive AbTPO, thyroid hypoechoic pattern, and thyroid volume < 6 mL were significantly higher in the SSc group than in controls. Two cases of papillary thyroid cancer (suspected by FNA and confirmed by histology) were observed in SSc, while none in controls (**Table 1**).

The prevalence and the incidence of new cases of thyroid disorders is reported in **Table 2**. Thyroid dysfunction, subclinical hypothyroidism, hypothyroidism, AbTPO positivity and a thyroid hypoechoic pattern were significantly more frequent in SSc than in controls.

Among the 23 patients who developed thyroid dysfunction during the follow-up, 11 (48%) showed cutaneous diffuse SSc and 12 (52%) the limited variant; visceral involvement included: peripheral vascular system, 91%; gastrointestinal system, 52%; lung, 65%; joint/tendons, 22%; heart, 30%; kidney, 9%; any statistical signicant difference was observed with respect to SSc patients without thyroid dysfunction. The prevalence of autoantibodies was: antinuclear 96%, anticentromere 30%, anti-Scl-70 48%; no statistical significant difference was observed with respect to SSc patients without thyroid dysfunction. In fact, the proportions of antinuclear, anticentromere, anti-Scl-70 autoantibodies in the SSc group who developed thyroid dysfunction (98%, 28%, 52%, respectively),

were not significantly different from the corresponding proportions in the SSc group who did not develop thyroid dysfunction (95%, 31%, 45%; respectively).

In SSc patients at the end of the follow-up, hypothyroidism was significantly associated with presence of AbTPO-positivity ($P < 0.0001$), a small thyroid volume (< 6 mL) ($P < 0.0001$), and a hypoechoic pattern ($P < 0.0001$) (all by χ^2); no relationship was found with the other thyroid parameters. Moreover, no significant association was observed among the cutaneous or visceral involvement or the presence of SSc specific autoantibodies and thyroid autoantibodies, or others of the studied parameters.

The number of euthyroid SSc patients and controls who were "thyroid autoantibody negative and with a nodule-free thyroid of normal echogenicity" ("clean") were respectively 83, and 75. The number of new cases of subclinical hypothyroidism or hyperthyroidism in these "clean" SSc patients were 3, and 1, respectively (4/83=5%), while in "clean" controls they were, 1 and 0, respectively (1/75=1%); the difference was not statistically significant. No other dysfunctions were observed in the "clean" patients.

In SSc women, the logistic regression analysis [in a model including, age, smoking, TSH value, AbTPO positivity, AbTg positivity, thyroid hypoechogenicity (presence/absence), thyroid volume (all at the start of evaluation) as independent variables, and hypothyroidism at last evaluation as dependent variable] shows that the appearance of hypothyroidism was related to a border line high initial TSH [coefficient, 0.859; Exp(coef), 2.361; 95% lower, 1.022; 95% upper, 5.455; $P = 0.0443$], AbTPO positivity [coefficient, 0.735; Exp(coef), 2.085; 95% lower, 1.154; 95% upper, 3.767; $P = 0.0150$], a hypoechoic pattern [coefficient, 0.919; Exp(coef), 2.506; 95% lower, 1.480; 95% upper, 4.245; $P = 0.0006$], and a small thyroid volume [coefficient, -0.155; Exp(coef), 0.857; 95% lower, 0.806; 95% upper, 0.911; $P < 0.0001$].

Discussion

Our study demonstrates a high incidence of new cases of hypothyroidism, thyroid dysfunction, AbTPO positivity, and appearance of a hypoechoic thyroid pattern in SSc women (15.5, 21, 11,

158 14.6/1000 SSc per year; respectively) in comparison with the control group, with similar urinary
159 iodine excretion.
160 It should be stressed that the incidence of new cases of hypothyroidism and AbTPO in the control
161 group was similar to that observed in other epidemiological studies (12-14), suggesting that the
162 control group is not biased, versus a low thyroid autoimmunity.
163 Interestingly, mean TSH value, the percentage of antithyroid antibodies, thyroid hypoechoic pattern
164 and small thyroid volume, were all significantly higher in SSc than in controls, in agreement with
165 other studies, and our previous transversal study (3).
166 The results of the logistic regression analysis show that in SSc women the appearance of
167 hypothyroidism was related to a border line high (even if in the normal range) TSH, the presence of
168 AbTPO positivity, a hypoechoic pattern, and a small thyroid volume, in agreement with the results of
169 other studies in the general population (12-14).
170 The baseline significant differences between SSc patients and controls, in the above mentioned
171 parameters, may account at least in part for the higher incidence of hypothyroidism in the SSc group.
172 However, interestingly, the prevalence of thyroid dysfunction in SSc patients and controls who were
173 “thyroid autoantibody negative and with a nodule-free thyroid of normal echogenicity” (“clean” SSc
174 patients) at the end of the study (5%) was higher than in “clean” controls (1%), even if the statistical
175 significance was not reached. This may suggest that also “clean” SSc patients should be periodically
176 surveyed for thyroid function.
177 The association of autoimmune disorders is a well known phenomenon (15). The pathogenetic base of
178 this association is under debate. Many evidence accumulated from animal models and available in
179 human diseases favor a prevalent Th1 lymphokine profile in target organs of patients with chronic
180 autoimmune thyroiditis, or Graves' ophthalmopathy (16), in the initial phase of these disorders.
181 Similarly, a prevalent Th1 immune reactivity is present in the initial phase of SSc, that switches to a
182 prevalent Th2 immune response later (17-20). This prevalence of the Th1 immune reactivity in the
183 initial phase of both SSc, and autoimmune thyroiditis, might be the common base that, under the
184 combined action of genetic and environmental conditions, may lead to the appearance of autoimmune
185 phenomena that involve different organs in the same subject (15).

In conclusion, our study shows a high incidence of new cases of hypothyroidism, thyroid dysfunction, AbTPO positivity, and appearance of a hypoechoic thyroid pattern in SSc women in comparison with the control group. However, similar studies performed in other European and non-European countries are necessary to confirm these results. Risk factors for the development of thyroid dysfunction are a border line high (even if in the normal range) TSH, the presence of AbTPO positivity, a hypoechoic pattern, and a small thyroid volume. Thyroid function and ultrasonography should be tested as a part of the clinical profile in female SSc patients. Those who are at high risk [a border line high (even if in the normal range) TSH, positive AbTPO, hypoechoic and small thyroid] should have periodically (approximately every year) thyroid function follow-up and appropriate treatment in due course.

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Table 1. Comparison of thyroid status at the initial, or at the last evaluation, between Systemic Sclerosis (SSc) patients and matched controls.

	Initial thyroid status			Last evaluation		
	SSc	Controls	*P*	SSc	Controls	*P*
N°	179	179		179	179	
Age, y (SD)	50 (13)	52 (10)	ns	56 (13)	60 (10)	ns
Gender (female)	179	179	ns	179	179	ns
TSH, μU/mL (SD)	2.1 (0.7)[b]	1.1 (0.6)	0.043[a]	2.9 (4.1)[b]	1.3 (1.1)	0.018[a]
FT4, pmol/L (SD)	115 (4.1)	122 (3.1)	ns	110 (4.6)	121 (3.4)	ns
FT3, pmol/L (SD)	4.7 (1.9)	5.0 (1.1)	ns	4.5 (1.9)	4.9 (1.2)	ns
AbTg, IU/mL (SD)	72 (134)	27 (85)	ns	94 (215)	36 (96)	ns
AbTPO, IU/mL (SD)	91 (169)[b]	15 (35)	0.026[a]	125 (256)[b]	23 (52)	0.013[a]
Subclinical hypothyroidism	0%	0%	ns	7.8%	1.7%	0.006[c]
Clinical hypothyroidism	0%	0%	ns	1.7%	0.56%	ns
Subclinical hyperthyroidism	0%	0%	ns	2.2%	1.7%	ns
Graves' disease	0%	0%	ns	1.1%	0%	ns
Thyroid dysfunctions	0%	0%	ns	13%	4%	0.001[c]
$AbTg^+$	11%	7%	ns	13%	9%	ns
$AbTPO^+$	21%	12%	0.022[c]	27%	13%	0.002[c]
Hypoechoic pattern	23%	12%	0.008[c]	32%	15%	<0.0001[c]
Thyroid autoimmunity	24%	12%	0.002[c]	34%	16%	<0.001[c]
Thyroid volume, mL (SD)	11 (10)	14 (13)	0.044[a]	10 (11)	14 (12)	0.037[a]
Thyroid volume > 20 mL	11%	13%	ns	11%	14%	ns
Thyroid volume < 6 mL	12%	5%	0.015[c]	16%	6%	0.004[c]
Thyroid nodules	39%	43%	ns	44%	50%	ns
Thyroid cancer	0%	0%	ns	1.1%	0%	ns

TSH = thyroid stimulating hormone; AbTPO = anti-thyroperoxidase antibody; $AbTPO^+$ = anti-thyroperoxidase antibodies >100 IU/ml; AbTg = anti-thyroglobulin antibody; $AbTg^+$ = anti-thyroglobulin antibodies >100 IU/ml; FT3 = free triiodothyronine; FT4 = free thyroxine; $AbTg^+$ or $AbTPO^+$ or ultrasonographic diagnosis of thyroiditis = thyroid autoimmunity. [a] = ANOVA. [b] = TSH levels and AbTPO titers were significantly higher in SSc than in controls. [c] = χ^2. Conversion factors for SI units: FT4 = 12.871; FT3 = 0.0154.

Table 2. New cases and incidence[a] of thyroid disorders in Systemic Sclerosis at the last evaluation.

	Systemic Sclerosis number new cases (incidence)	**Controls** number new cases (incidence)	***P***[b]
Subclinical hypothyroidism	14 (12.8)	3 (2.1)	0.006
Clinical hypothyroidism	3 (2.7)	1 (0.7)	ns
Hypothyroidism	17 (15.5)	4 (2.8)	0.003
Subclinical hyperthyroidism	4 (3.6)	3 (2.1)	ns
Graves' disease	2 (1.8)	0 (0)	ns
Hyperthyroidism	6 (5.4)	3 (2.1)	ns
Thyroid dysfunction	23 (21)	7 (4.2)	0.001
$AbTg^+$	4 (3.6)	3 (2.1)	ns
$AbTPO^+$	11 (11)	3 (2.8)	0.04
Hypoechoic pattern	16 (14.6)	5 (3.5)	0.013
Thyroid volume > 20 mL	0 (0)	2 (1.4)	ns
Thyroid volume < 6 mL	6 (5.4)	2 (1.4)	ns
Thyroid nodules	9 (8.2)	12 (8.5)	ns

[a] Incidence is reported in parenthesis. Incidence = [incidence = number of new cases / patients (179) x years of follow-up (73 months = 6.1 years) = number of new events / 1092 patients per year)] and matched controls (C) [incidence = number of new cases / subjects (179) x years of follow-up (94 months = 7.8 years) = number of new events / 1396 patients per year)].

[b] = χ^2 (number of new cases).

AbTPO = anti-thyroperoxidase antibody; $AbTPO^+$ = anti-thyroperoxidase antibodies >100 IU/mL; AbTg = anti-thyroglobulin antibody; $AbTg^+$ = anti-thyroglobulin antibodies >100 IU/mL.