

1 **Incidence of Thyroid Disorders in Systemic Sclerosis:** 2 **results from a longitudinal follow-up.**

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4 Alessandro Antonelli¹, Poupak Fallahi¹, Silvia Martina Ferrari¹, Caterina Mancusi¹,
5 Dilia Giuggioli², Michele Colaci², Clodoveo Ferri².

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7 ¹ Department of Clinical and Experimental Medicine, University of Pisa, Via Savi 10, 56126 Pisa,
8 Italy;

9 ² Department of Medical, Surgical, Maternal, Pediatric and Adult Sciences, University of Modena &
10 Reggio Emilia, Via del Pozzo 71, 41100 Modena, Italy.

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12 **Abbreviated Title:** Incidence of thyroid disorders in scleroderma

13 **Key terms:** Systemic Sclerosis, Thyroid autoimmunity, Hypothyroidism, Scleroderma, Thyroid
14 nodules

15 **Word count:** 1800

16 **Number of figures and tables:** 2

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18 *Corresponding author and person to whom reprint requests should be addressed:*

19 Alessandro Antonelli, MD
20 Department of Clinical and Experimental Medicine
21 University of Pisa
22 Via Savi 10, I-56126, Pisa, Italy
23 Phone: +39-050-992318
24 Fax: +39-050-553235
25 e-mail: alessandro.antonelli@med.unipi.it

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27 **Disclosure Statement:** The authors have nothing to disclose

29 **Abstract**

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

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

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

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

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

51

51 **Introduction**

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

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

57

58 **Patients and Methods**

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

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

66 Skin sclerosis was observed in all patients (diffuse 43, or limited 57%; visceral involvement included:
67 peripheral vascular system, 93%; gastrointestinal system, 55%; lung, 64%; joint/tendons, 24%; heart,
68 27%; kidney, 13%). The prevalence of autoantibodies (2,3) was: antinuclear 92%, anticentromere
69 35%, anti-topoisomerase I (anti-Scl-70) 44%.

70 Each of the 179 female SSc patients eligible for the study was gender- and age-matched, one-to-one
71 with a control group, without thyroid dysfunction, of the background population from the same
72 geographic area (North-West Tuscany) (8). This control group was extracted from a larger sample of
73 1081 subjects in a population-based survey of thyroid disorders, who were initially studied in 1994
74 and subsequently reevaluated (by thyroid function, autoantibodies and ultrasonography) in 2002-2003
75 (see above).

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

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

80 The mean follow-up period from the initial evaluation was 95 months (range 87-106 months, median
81 94 months). All SSc patients and controls were reevaluated, by: a- physical examination; b- thyroid
82 ultrasonography, as previously reported (11); c- thyroid nodules with a diameter > 10 mm were
83 submitted to ultrasonography-guided fine-needle aspiration (FNA) (11); d- circulating free T3 (FT3)
84 and free T4 (FT4) (AMERLEX-MAB FT3/FT4 Kit; Amersham, UK), TSH (reference range 0.3-3.6
85 $\mu\text{U}/\text{mL}$) (DiaSorin, USA), anti-thyroperoxidase (AbTPO) and anti-thyroglobulin (AbTg) antibodies
86 (ICN Pharmaceuticals, USA; positivity > 100 IU/mL). Anti-TSH-receptor antibodies (TRAb) were
87 measured in patients with hyperthyroidism (Radim, Italy; normal range 0-1 IU/mL).

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

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

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

97

98 **Results**

99 *Longitudinal study*

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

102 UIE in SSc patients and in controls was not significantly different (median 87.0 $\mu\text{g}/\text{L}$, IR 39.0–143.5
103 $\mu\text{g}/\text{L}$; median 79.0 $\mu\text{g}/\text{L}$, IR 34.3–138.6 $\mu\text{g}/\text{L}$, respectively; $P = \text{ns}$).

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

109 At the last evaluation (after a median of 73 and 94 months, respectively in SSc and controls: $P < 0.01$,
110 ANOVA) TSH levels and AbTPO titers were significantly higher in SSc than in controls (**Table 1**).
111 Subclinical hypothyroidism was significantly more common in SSc than in controls, while clinical
112 hypothyroidism did not reach the significance. Two cases of Graves' disease were observed in SSc
113 patients, while no case was observed in controls. The prevalence of subclinical hyperthyroidism was
114 similar in SSc and controls. On the whole the prevalence of thyroid dysfunction (subclinical or
115 clinical hypo- and hyper-thyroidism) was significantly more frequent in SSc patients (**Table 1**). The
116 prevalence of subjects with positive AbTPO, thyroid hypoechoic pattern, and thyroid volume < 6 mL
117 were significantly higher in the SSc group than in controls. Two cases of papillary thyroid cancer
118 (suspected by FNA and confirmed by histology) were observed in SSc, while none in controls (**Table**
119 **1**).

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

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

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

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

139 The number of euthyroid SSc patients and controls who were “thyroid autoantibody negative and with
140 a nodule-free thyroid of normal echogenicity” (“clean”) were respectively 83, and 75. The number of
141 new cases of subclinical hypothyroidism or hyperthyroidism in these “clean” SSc patients were 3, and
142 1, respectively (4/83=5%), while in “clean” controls they were, 1 and 0, respectively (1/75=1%); the
143 difference was not statistically significant. No other dysfunctions were observed in the “clean”
144 patients.

145 In SSc women, the logistic regression analysis [in a model including, age, smoking, TSH value,
146 AbTPO positivity, AbTg positivity, thyroid hypoechogenicity (presence/absence), thyroid volume (all
147 at the start of evaluation) as independent variables, and hypothyroidism at last evaluation as
148 dependent variable] shows that the appearance of hypothyroidism was related to a border line high
149 initial TSH [coefficient, 0.859; Exp(coef), 2.361; 95% lower, 1.022; 95% upper, 5.455; $P = 0.0443$],
150 AbTPO positivity [coefficient, 0.735; Exp(coef), 2.085; 95% lower, 1.154; 95% upper, 3.767; $P =$
151 0.0150], a hypoechoic pattern [coefficient, 0.919; Exp(coef), 2.506; 95% lower, 1.480; 95% upper,
152 4.245; $P = 0.0006$], and a small thyroid volume [coefficient, -0.155; Exp(coef), 0.857; 95% lower,
153 0.806; 95% upper, 0.911; $P < 0.0001$].

154

155 **Discussion**

156 Our study demonstrates a high incidence of new cases of hypothyroidism, thyroid dysfunction,
157 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).

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

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

	<u>Initial thyroid status</u>			<u>Last evaluation</u>		
	SSc	Controls	<i>P</i>	SSc	Controls	<i>P</i>
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, μ U/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

275 TSH = thyroid stimulating hormone; AbTPO = anti-thyroperoxidase antibody; AbTPO⁺ = anti-
 276 thyroperoxidase antibodies >100 IU/ml; AbTg = anti-thyroglobulin antibody; AbTg⁺ = anti-
 277 thyroglobulin antibodies >100 IU/ml; FT3 = free triiodothyronine; FT4 = free thyroxine; AbTg⁺ or
 278 AbTPO⁺ or ultrasonographic diagnosis of thyroiditis = thyroid autoimmunity. ^a = ANOVA. ^b = TSH
 279 levels and AbTPO titers were significantly higher in SSc than in controls. ^c = χ^2 . Conversion factors
 280 for SI units: FT4 = 12.871; FT3 = 0.0154.
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282 **Table 2. New cases and incidence^a of thyroid disorders in Systemic Sclerosis at the last**
 283 **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

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

288 ^b = χ^2 (number of new cases).

289 AbTPO = anti-thyropoxidase antibody; AbTPO⁺ = anti-thyropoxidase antibodies >100 IU/mL;
 290 AbTg = anti-thyroglobulin antibody; AbTg⁺ = anti-thyroglobulin antibodies >100 IU/mL.

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