Clinical and subclinical autoimmune thyroid disorders in systemic sclerosis

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Abstract

Objective: Several studies have reported the association of systemic sclerosis (SSc) with thyroid autoimmune disorders, but most of them have neither an appropriate control group nor include a complete thyroid work-up.

Design: The aim of our study was to evaluate the prevalence of thyroid disorders in a large number of patients with SSc using a complete clinical evaluation.

Methods: Thyroid-stimulating hormone (TSH), free triiodothyronine, free thyroxine, antithyroglobulin and antithyroid-peroxidase (AbTPO) autoantibodies, thyroid ultrasonography and blood flow and fine needle aspiration were performed in 202 SSc patients versus 404 gender- and age-matched controls from the general population, with similar iodine intake, to evaluate the prevalence of clinical and subclinical thyroid disorders.

Results: Odds ratio (OR) for female SSc versus controls was: for subclinical hypothyroidism, 3.2 (95% CI = 1.8–5.7); for clinical hypothyroidism, 14.5 (95% CI = 2.3–90.9); for AbTPO positivity, 2.7 (95% CI = 1.8–4.1); for hypoechoic pattern, 3.2 (95% CI = 2.2–4.7); for thyroid autoimmunity, 3.7 (95% CI = 2.6–5.4); for thyroid volume < 6 ml, 1.8 (95% CI = 1.2–2.7). OR for thyroid autoimmunity in male SSc versus controls was 10.8 (95% CI = 2.2–52.4). Mean values of TSH in female SSc, and of AbTPO in female and male SSc were higher (P<0.01) than in controls. We observed three cases of Graves' disease in female SSc versus zero in controls (P<0.014), and two cases of papillary thyroid cancer in SSc patients.

Conclusions: Thyroid function, AbTPO and ultrasonography should be tested as part of the clinical profile in SSc patients. Females, subjects with positive AbTPO and hypoechoic and small thyroid should have thyroid function follow-up and appropriate treatment in due course.

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Introduction

Progressive systemic sclerosis (SSc) or diffuse scleroderma is a connective tissue disease of unknown etiology, characterized by vascular abnormalities, multiorgan fibrosis and complex immune system alterations (1–6).

The association of SSc with thyroid fibrosis (7, 8), hypothyroidism (8–15) and thyroid autoimmunity (8–19) has been reported by several studies in a wide range of variability. However, most of them do not have an appropriate control group to evaluate the relative risk or odds ratio (OR) of hypothyroidism (8–14), even if three of them reported a higher mean TSH level in SSc patients than in controls (10, 12, 13). Furthermore, none take into account iodine intake, which is a major determinant of thyroid disorders, and do not include a complete thyroid work-up (thyroid scan was evaluated only in the study by De Keyser et al. (12), while thyroid ultrasonography, which has been progressively becoming one of the most important tools in the diagnosis of thyroid disorders, has never been evaluated in SSc patients). For other thyroid disorders such as Graves' disease (20–22), central hypothyroidism (23), euthyroid sick syndrome (24), thyroid nodules and thyroid cancer (23, 25, 26) only anecdotal reports are present in the literature.

The aim of our study was to evaluate the prevalence of clinical and subclinical thyroid disorders in a wide group of patients with SSc by assessing thyroid morphology at ultrasound examination and detecting thyroid hormones and antithyroid autoantibodies, in comparison with an age- and sex-matched control group from the same geographic area with a similar status of iodine intake (27).
Materials and methods

Subjects

SSc patients In total, 202 SSc patients consecutively referred to the Rheumatology Units of the Universities of Pisa and Modena (from 1999 to 2004) were recruited into the study. SSc was classified according to the American College of Rheumatology 1980 preliminary criteria (5). Standardized criteria were followed for the evaluation of clinico-serological features, main visceral organ involvement and disease activity as previously described (3, 4). Skin sclerosis was observed in all patients (diffuse 16%, intermediate 25% or limited 59%); visceral involvement included: peripheral vascular system, 93%; gastrointestinal system, 56%; lung, 62%; joint/tendons, 18%; heart, 31%; kidney, 8%. The prevalence of autoantibodies, evaluated according to standard methodologies (3), was: antinuclear 93%, anticentromere 35%, antitopoiso-merase I (anti-Scl-70) 39%.

Control group – general population Each of the SSc patients eligible for the study was matched, by sex and age, one-to-two with a control group of subjects of the background population from the same geographic area (North-West Tuscany). This control group was extracted from a larger sample of 1640 subjects in a population-based survey of thyroid disorders (28, 29). Iodine intake differs within Tuscany, and reliable data on local iodine intake based on urinary iodine excretion are available (27). Extraction of either control group from the original populations was performed by finding the closest age match (±3 years) to each case within either gender. When more than one age-match was available per case, the choice was made at random. Subjects with history of rheumatic diseases or with symptoms or signs of rheumatic disorders at physical examination were excluded from the control group.

Patients or controls on medications that may influence thyroid function (i.e. amiodarone, lithium, etc.) were preliminarily excluded from the study (three patients and two controls). All patients and controls underwent a complete clinical evaluation, with special attention paid to risk factors for thyroid disorders (family history of thyroid disease, residence in iodine-deficient areas and smoking habits). The SSc patients and controls had similar gender distributions (females/males: 91/9% in both SSc and controls) and mean age (55 ± 13 vs 54 ± 9 years respectively) by the matching procedure; no significant difference was observed regarding family history of thyroid disease (41 and 43% respectively) or smoking habit (19 and 23% respectively). The majority of SSc and control subjects had resided in an iodine-deficient area for 20 years or more (78% vs 82% respectively), without any significant difference between the two groups.

Methods

Neck ultrasonography and fine-needle aspiration Thyroid ultrasonography was performed both in patients and in controls. Neck ultrasonography was performed by the same (blinded) operator using a Esaote AU5 (Florence, Italy) with a sectorial 7.5 MHz transducer. Thyroid volume was calculated using the ellipsoid formula, as described (30–32). The presence of hypoechoic and dyshomogeneous echogenicity was arbitrarily rated at three levels (0, normal echogenicity; 1, slight hypoechoic and dyshomogeneous pattern; 2, severely hypoechoic and dyshomogeneous pattern) in order to evaluate structural abnormalities of thyroid tissue associated with thyroid autoimmunity (30–32). The presence of thyroid nodules was recorded; nodules with a diameter >10 mm were submitted to ultrasonography-guided fine-needle aspiration (FNA), which was performed by the same operator using a free-hand method, as already described (30–32).

Thyroid blood flow Thyroid blood flow (TBF) was studied in all patients by color-flow Doppler (CFD) (31–33). The CFD pattern was defined as follows: a) normal (or type 0) when TBF was limited to peripheral thyroid arteries; b) type I when TBF was mildly increased; c) type II when TBF was clearly increased; d) type III when TBF was markedly increased (31–33).

Laboratory evaluation This included measurement of serum levels of thyroid-stimulating hormone (TSH; reference range 0.3–3.6 μU/ml), free triiodothyronine (FT3), free thyroxine (FT4), antithyroglobulin (AbTg) and antithyroid peroxidase antibody titers (AbTPO). Circulating FT3 and FT4 were measured by commercial RIA kits (AMERLEX-MAB FT3/FT4 Kit; Amersham). Serum TSH (DiaSorin, Stillwater, MN, USA), AbTPO and AbTg (ICN Pharmaceuticals, Costa Mesa, CA, USA) were evaluated by IRMA methods. For AbTg and AbTPO positivity was set at >100 IU/ml and >100 IU/ml respectively. Values are given as mean ±s.d. for normally distributed variables. AntiTSH-receptor autoantibodies (TRAab) were measured in patients with the use of a radioreceptor assay (Radim, Pomezia, Italy; normal range 0–1 IU/ml).

The study was approved by the institutional ethics committee, and all subjects gave their informed written consent to participate.
**Statistical analysis** Since female gender is a well-recognized risk factor for thyroid disorders, levels of TSH, FT\(_3\), FT\(_4\), AbTPO and AbTg were compared only among subjects of the same gender. Mean group values were compared by using one-way ANOVA for normally distributed variables, otherwise by the Mann–Whitney U test. The \(\chi^2\)-test or the OR were used to compare categorical variables.

**Results**

**Results in female SSc and female controls**

TSH levels and AbTPO titers were significantly higher in SSc than in control women (Table 1). Subclinical hypothyroidism (defined as TSH > 3.6 \(\mu\)U/ml with FT\(_4\) and FT\(_3\) within normal range) and clinical hypothyroidism (defined as TSH > 3.6 \(\mu\)U/ml with FT\(_4\) below the normal range) were significantly more common in SSc than in controls. The mean value of TSH was 4.5 \pm 2.0 \(\mu\)U/ml (range 3.6–14.4) in SSc with subclinical hypothyroidism, 34.2 \pm 48.0 \(\mu\)U/ml (range 14.6–143.5) in patients with clinical hypothyroidism and 5.6 \pm 2.2 \(\mu\)U/ml (range 3.6–11.1) in controls with subclinical hypothyroidism. The prevalence of subjects with positive AbTPO was significantly higher in the SSc group than in controls. A thyroid hypoechoic pattern, often a sign of inflammatory involvement of thyroid tissue (30–32), was more frequent in SSc than in controls. Thyroid autoimmunity was diagnosed by ultrasonography in the absence of positive AbTg or AbTPO in 12 SSc (six with subclinical hypothyroidism and two with clinical hypothyroidism) and in two controls. On the whole, indices of thyroid autoimmunity (AbTg, AbTPO or ultrasonographic diagnosis of thyroiditis) were significantly more frequent in SSc than in controls (Fig. 1). In contrast, there was no statistically significant difference in the prevalence of subclinical hyperthyroidism (defined as TSH < 0.2 \(\mu\)U/ml with FT\(_4\) and FT\(_3\) within normal range) between the two groups (Table 1). The prevalence of Graves’ disease (30–32) [established from the clinical presentation: presence of a diffuse goiter (varying in size from normal to very large), thyroid hormones (clinical hyperthyroidism defined as TSH < 0.2 \(\mu\)U/ml with FT\(_3\) above the normal range), thyroid autoantibodies measurements (presence of TRAb), thyroid ultrasonography (decreased, dyshomogeneous echogenicity, and diffuse goiter), and thyroid scan (diffuse uptake in the thyroid)] was significantly higher in SSc than in controls (Table 1). Thyroid volume was significantly lower and a small thyroid (defined as thyroid volume < 6 ml) was significantly more frequent in SSc than in controls. Thyroid enlargement (defined as a thyroid volume > 20 ml) was not significantly different in the two groups, as was the prevalence of thyroid nodules.

One case of papillary thyroid cancer (suspected by FNA and confirmed by histology) was observed in female SSc, with none in controls.

**Table 1** Comparison of thyroid status between female patients with systemic sclerosis (SSc) and female controls (C).

<table>
<thead>
<tr>
<th></th>
<th>SSc</th>
<th>C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>184</td>
<td>368</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 \pm 12</td>
<td>54 \pm 9</td>
<td>NS</td>
</tr>
<tr>
<td>TSH ((\mu)U/ml)</td>
<td>3.6 \pm 1.6*</td>
<td>1.6 \pm 1.4</td>
<td>0.0013</td>
</tr>
<tr>
<td>FT(_4) (pmol/l)</td>
<td>115 \pm 5.1</td>
<td>117 \pm 26</td>
<td>NS</td>
</tr>
<tr>
<td>FT(_3) (pmol/l)</td>
<td>4.6 \pm 1.5</td>
<td>4.8 \pm 2</td>
<td>NS</td>
</tr>
<tr>
<td>AbTg (IU/ml)</td>
<td>121 \pm 207</td>
<td>68 \pm 206</td>
<td>NS</td>
</tr>
<tr>
<td>AbTPO (IU/ml)</td>
<td>115 \pm 491*</td>
<td>24 \pm 62</td>
<td>0.0005</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>31/153 (17%)</td>
<td>22/346 (6%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Clinical hypothyroidism</td>
<td>7/177 (4%)</td>
<td>1/367 (0.3%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>6/178 (3.3%)</td>
<td>22/346 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>3 (1.6%)</td>
<td>0</td>
<td>0.0140</td>
</tr>
<tr>
<td>AbTg*</td>
<td>35/149 (19%)</td>
<td>59/309 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>AbTPO*</td>
<td>72/112 (39%)</td>
<td>70/298 (19%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypoechoic pattern</td>
<td>88/96 (48%)</td>
<td>81/287 (22%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Thyroid autoimmunity</td>
<td>107/77 (58%)</td>
<td>100/268 (27%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Thyroid volume (ml)</td>
<td>10 \pm 9</td>
<td>13 \pm 14</td>
<td>0.0156</td>
</tr>
<tr>
<td>Thyroid volume &gt; 20 ml</td>
<td>21/163 (11%)</td>
<td>44/324 (12%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thyroid volume &lt; 6 ml</td>
<td>54/130 (29%)</td>
<td>70/298 (19%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Thyroid nodules</td>
<td>96/88 (52%)</td>
<td>210/158 (57%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Thyroid stimulating hormone, TSH; Antithyroperoxidase antibody, AbTPO; antithyroperoxidase antibodies > 100 IU/ml, AbTPO*; antithyroglobulin antibody, AbTg, antithyroglobulin antibodies > 100 IU/ml, AbTg*; free triiodothyronine, FT\(_3\); free thyroxine, FT\(_4\); thyroid autoimmunity, AbTg or AbTPO* or ultrasonographic diagnosis of thyroiditis.

**Figure 1** The prevalence of AbTPO positivity (AbTPO+) subclinical hypothyroidism and thyroid autoimmunity in female SSc patients was significantly higher than in controls (\(P<0.05, \chi^2\)).
The OR for female SSc with respect to controls was: for subclinical hypothyroidism, 3.2 (95% CI, 1.8–5.7); for clinical hypothyroidism, 14.5 (95% CI, 2.3–90.9); for AbTPO positivity, 2.7 (95% CI, 1.8–4.1); for hypoechoic pattern, 3.2 (95% CI, 2.2–4.7); for thyroid autoimmunity, 3.7 (95% CI, 2.6–5.4); for thyroid volume < 6 ml, 1.8 (95% CI, 1.2–2.7).

Results in male SSc and male controls

The prevalence of male patients with positive AbTPO and the AbTPO titer in SSc were significantly higher than in controls (Table 2). Thyroid autoimmunity was diagnosed by ultrasonography in the absence of positive AbTg and AbTPO in two SSc and one control. On the whole, indices of thyroid autoimmunity (AbTg, AbTPO, or ultrasonographic diagnosis of thyroiditis) were significantly more frequent in SSc than in controls. One case of papillary thyroid cancer (suspected by FNA and confirmed by histology) was observed in one SSc, with none in controls. No case of clinical hypothyroidism or hyperthyroidism was observed. The OR for male patients with SSc with respect to controls for thyroid autoimmunity was 10.8 (95% CI, 2.2–52.4).

General results

In each group (Tables 1 and 2) any kind of thyroid disorders had a higher prevalence in women than in men, with the exception of thyroid enlargement (defined as thyroid volume > 20 ml). Thyroid enlargement was more frequent in men, as expected since thyroid volume is physiologically higher in men (30–32), but no significant difference was shown in their prevalence between SSc and control males (Tables 1 and 2).

SSc patients with thyroid autoimmunity had a longer disease duration than other SSc (16 ± 11 vs 9 ± 7 years, P < 0.05), while no relationship between disease activity and any kind of thyroid disorders was observed. No significant association was observed among the cutaneous or visceral involvement or the presence of SSc-specific autoantibodies, and thyroid dysfunctions or thyroid autoantibodies.

Pooling the data of female and male SSc patients, thyroid enlargement was significantly associated with the presence of thyroid nodules (presence of nodules 92% vs 44%, in presence or absence of goiter respectively; P = 0.0012), while the frequency of patients with positive AbTPO (40% vs 36%, in presence or absence of goiter respectively) or AbTg (25% vs 17%, in presence or absence of goiter respectively) was higher in presence of goiter, even if it did not reach statistical significance: the prevalence of hypothyroidism was lower in presence of goiter (8%) than in absence of goiter (25%), even if not significantly (no relationship was found with the other thyroid parameters).

In SSc patients (Table 3), hypothyroidism was significantly associated with the presence of a small thyroid volume (< 6 ml) and a hypoechoic pattern (no relationship was found with the other thyroid parameters). FNA was performed in 28 SSc patients (14%) and in 54 controls (13.4%). Benign thyroid lesions at cytology were found in 24 SSc patients (86%) and in 48 controls (89%); two cases of papillary thyroid cancer (suspected by FNA and confirmed by histology) were observed in SSc, with none in controls; the remainders were not diagnostic (without any significant difference between the groups).

In controls (Table 4), hypothyroidism was significantly associated with the presence of AbTPO, AbTg, a low thyroid volume (< 6 ml) and a hypoechoic pattern (no relationship was found with the other thyroid parameters). Comparing hypothyroid SSc and controls, a significantly higher prevalence of a thyroid hypoechoic pattern was observed in SSc (79% vs 21%), than in controls (48% vs 52%; P = 0.0243; no relationship was found with the other thyroid parameters).

In controls with autoimmune thyroid disorders, TBF bore no relation to the thyroid status and was type 0 in 60%, type I in 33%, type II in 7% subjects, while none had type III CFD pattern; a similar pattern was observed in SSc patients (type 0 in 54%, type I in 35%, type II in 11%, and type III in 0% of patients) with thyroid autoimmunity, without any statistical difference.

Two cases of euthyroid sick syndrome (24) and no cases of central hypothyroidism (23) were observed in SSc, with none in controls.
**Table 3** Relationship between hypothyroidism (TSH > 3.6 μU/ml) and other thyroid parameters in SSc patients (female and male).

<table>
<thead>
<tr>
<th></th>
<th>TSH &gt; 3.6 μU/ml (%)</th>
<th>TSH &lt; 3.6 μU/ml (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbTPO &gt; 10 IU/ml</td>
<td>46</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>AbTPO &lt; 10 IU/ml</td>
<td>54</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Thyroid volume &lt; 6 ml</td>
<td>42</td>
<td>22</td>
<td>0.0381</td>
</tr>
<tr>
<td>Thyroid volume &gt; 6 ml</td>
<td>58</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Hypoechoic pattern YES</td>
<td>79</td>
<td>33</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypoechoic pattern NO</td>
<td>21</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

Antithyroid peroxidase antibody, AbTPO; *χ².

**Discussion**

Previous clinical studies demonstrated a high prevalence of hypothyroidism in SSc: the prevalence of clinical hypothyroidism ranged from 2.4 to 26%, while that of subclinical hypothyroidism ranged from 3.5 to 26% (8–14). None of these studies had an appropriate control; furthermore other parameters such as iodine status and thyroid morphology were not studied. More recently Innocencio et al. (15) studied 25 SSc patients in comparison with a control group of 113 healthy individuals, but no significant result relating to hypothyroidism was found, mainly because of the small number of SSc patients. The results of our study, using more tests and more sensitive methodology in a larger group of 202 SSc matched with 404 controls with a similar exposition to iodine deficiency, demonstrate a significantly higher OR for clinical and subclinical hypothyroidism (with a prevalence of 4 and 17% respectively) in female SSc than in controls. It should be stressed that the control was a sample of the general population of central Italy, so the present series is a case-control study and not an epidemiological survey. However, the prevalence of hypothyroidism in the control females was substantial (6%), similar or higher than that reported (5.8–8%) in some recent studies of SSc (14, 15) and fully in the range of the reported age-adjusted prevalence rates for the Italian population (29, 34). This indicates that the control was not biased towards a lower hypothyroidism prevalence in comparison with the general population and that the current results agree closely with those reported by a population-based survey so far in the literature (35), which showed a 8% prevalence for subclinical hypothyroidism in females over the age of 40 years (36). Interestingly, mean TSH value was significantly higher in SSc than in controls, in agreement with other studies (10, 12, 13).

Autoimmune phenomena are an almost constant feature of patients with SSc (1–6). The percentage of antithyroid antibodies ranged from 12 to 52% in different studies (8–19). This wide range may be at least partially explained by application of steroids and immune suppressive drugs in SSc, and by the different gender and age composition (23) and iodine intake of SSc patients. In most of the older studies AbTg were more common than antimicrosomal antibodies (11, 16–18), while in the more recent ones a higher prevalence of AbTPO was found (12–15). The results of our study demonstrate a significantly higher titer and prevalence of AbTPO, but not of AbTg, both in female and in male SSc than in controls. Population studies have shown the prevalence of AbTPO to be around 10% in females (range 10–15%), and it increases with age (from 8% in females over 18 years of age to about 30% in women over 70) (35, 36). In our female controls, the prevalence of AbTPO positivity was 19%, similar or higher than that reported in some studies in SSc (18–19%) (12, 14) and fully in the range of the reported age-adjusted prevalence rates for the Italian population (29, 34) and for other population-based surveys (35, 36). In female SSc the prevalence of AbTPO positivity was 39%, significantly higher. Similarly, an increased and significant prevalence (17%) of AbTPO positivity was shown in SSc males than in controls. The prevalence of AbTg from population studies have been reported to be around 10% in females (range 10–15%) (29, 34–36), which is similar to that observed in our female controls (16%), while in SSc the prevalence of AbTg positivity was 19% which is higher, even if not significant. Altogether, the above mentioned data indicate a higher prevalence of thyroid autoimmunity in SSc, overall of female gender, compared with controls.

The presence of antithyroid antibodies was found in about half of SSc with overt hypothyroidism (11), similar to what was found in our study for AbTPO (46%). However, a higher prevalence of fibrosis of the thyroid gland, not necessarily associated with the typical features of Hashimoto’s thyroiditis, has been described in SSc in several studies (7, 8, 23), suggesting that hypothyroidism in SSc might be due to the fibrosis per se that is the main feature of SSc, rather than to Hashimoto’s thyroiditis. This hypothesis is strengthened by our findings that hypothyroidism in SSc is significantly associated with a thyroid hypoechoic pattern and a small thyroid volume, but not with a higher prevalence of AbTg or AbTPO, which are instead significantly associated with hypothyroidism in

**Table 4** Relationship between hypothyroidism (TSH > 3.6 μU/ml) and other thyroid parameters in controls (female and male).

<table>
<thead>
<tr>
<th></th>
<th>TSH &gt; 3.6 μU/ml (%)</th>
<th>TSH &lt; 3.6 μU/ml (%)</th>
<th>P*</th>
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<tbody>
<tr>
<td>AbTg &gt; 50 IU/ml</td>
<td>33</td>
<td>15</td>
<td>0.0220</td>
</tr>
<tr>
<td>AbTg &lt; 50 IU/ml</td>
<td>67</td>
<td>85</td>
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<td>AbTPO &gt; 10 IU/ml</td>
<td>57</td>
<td>16</td>
<td>0.0001</td>
</tr>
<tr>
<td>AbTPO &lt; 10 IU/ml</td>
<td>43</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Thyroid volume &lt; 6 ml</td>
<td>47</td>
<td>16</td>
<td>0.0004</td>
</tr>
<tr>
<td>Thyroid volume &gt; 6 ml</td>
<td>53</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Hypoechoic pattern YES</td>
<td>48</td>
<td>18</td>
<td>0.0001</td>
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<tr>
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<td>52</td>
<td>82</td>
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<tr>
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<td>57</td>
<td>23</td>
<td>0.0004</td>
</tr>
<tr>
<td>Thyroid autoimmunity NO</td>
<td>43</td>
<td>77</td>
<td></td>
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Antithyroid peroxidase antibody, AbTPO; antithyroglobulin antibody, AbTg; *χ².
controls. Furthermore, comparing features specifically associated with hypothyroidism between SSc and controls, a significantly higher prevalence of thyroid hypoechocic pattern was observed in SSc (79% vs 48% respectively). These findings suggest that cellular immunity may be more important than humoral autoimmune reactions in the pathogenesis of hypothyroidism and thyroid fibrosis in SSc, and that ultrasonography is able to detect morphological alterations of the thyroid tissue that are associated with a higher risk of hypothyroidism.

Incidence of hyperthyroidism in SSc is unknown (20–23). In a study by Mourier-Claveul et al. in a group of 18 SSc, one with Graves’ disease was shown (25). In our study, a significantly higher prevalence of Graves’ disease is observed in female SSc, while no significant difference was observed for subclinical hypothyroidism, mainly related to nodular goiter with functionally autonomous nodules. It is noteworthy that no case of Graves’ disease was found among controls, similar to observations in other samples from the same population (37, 38).

We were not able to confirm a significantly high prevalence of central hypothyroidism (23) or of euthyroid sick syndrome (24) in SSc.

Thyroid volume in controls is fully in the range of the reported age-adjusted volume for the Italian population living in areas of slight iodine deficiency (29, 34) and is not significantly different from that observed in SSc, with similar exposition to iodine deficiency. In addition, the prevalence of thyroid nodules in SSc was similar to that observed in the general population (29, 34).

Single reports of association of SSc with thyroid cancer or adenoma have been published (8, 23, 25, 26). In our series of SSc, two cases of thyroid papillary cancer were detected, which is higher, even if not statistically so, than in controls. It is difficult to conclude the pathogenetical link between SSc and neoplasia, although such association has been suggested by some authors (23, 26). However, our data suggest a careful thyroid follow-up in SSc with thyroid nodules.

The association of autoimmune disorders is a well-known phenomenon (39, 40). The pathogenetic basis of this association is under debate. However, evidence accumulated from animal models and available in human diseases favor a prevalent Th1 lymphokine profile in target organs of patients with chronic autoimmune thyroiditis (31, 32) or Graves’ ophthalmopathy (41), while both Th1 and Th2 activation is present in SSc (42, 43). This common Th1 prevalence, under the combined action of genetic and environmental conditions, may involve different organs in the same subject, with the appearance of multiple immune-mediated disorders and leading to different clinical disorders (39, 40).

In conclusion, the results of our study of a large group of SSc demonstrate a significantly higher prevalence of AbTPO, ultrasonographic findings of thyroid autoimmunity, clinical and subclinical hypothyroidism, and Graves’ disease than in a very large group of controls with a similar iodine status. The diagnosis of thyroid dysfunction in SSc may have an important impact also on the clinical manifestations of SSc; in fact, Raynaud’s phenomenon is more difficult to control in hypothyroid individuals (44, 45), and pulmonary hypertension (46) can be seriously influenced by hemodynamic changes of hypothyroidism. Thyroid function and ultrasonography should be tested as a part of the clinical profiling of SSc patients. Those who are at high risk (females, positive AbTPO, hypoechocic and small thyroid patients) should have thyroid function follow-up and appropriate treatment in due course.

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