Thyroid Disorders in Patients with Systemic Sclerosis: Biochemical and Sonographic Characteristics. A Prospective Cohort Study

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ABSTRACT **Background:** Patients with systemic sclerosis (SSc) are at increased risk for autoimmune thyroid diseases, but information regarding thyroid nodules and cancer in SSc is scarce.

Objectives: To evaluate the thyroid gland in patients with SSc at a single Israeli center.

Methods: Thyroid workup was conducted in consecutive SSc patients: thyroid-stimulating hormone (TSH), free thyroxine (fT4), anti-thyroid peroxidase, and anti-thyroglobulin antibodies, as well as thyroid ultrasound and fine needle aspiration (FNA) when appropriate.

Results: Fifty patients, mean age 51.3 ± 13.5 years (44 women) were evaluated. Ten were previously diagnosed with thyroid disease. Median TSH level was 2.0 (normal range 0.23–4 mIU/l) and median fT4 level was 1.0 (normal range 0.8–2.0 ng/dl). Among the 40 thyroid disorder-naive patients, 3 had subclinical hypothyroidism and 5 had positive anti-thyroid antibodies; 22 (44%) had 1–6 thyroid nodules, which were ≥ 1 cm in 12 (24%). Accordingly, six patients underwent FNA, and five were diagnosed as colloid nodules and one as papillary carcinoma.

Conclusions: New cases of clinically significant autoimmune thyroid disease were not detected in our cohort of patients with SSc. Nevertheless, almost half had thyroid nodules. The clinical significance of these findings and their relation to thyroid cancer remains to be determined.

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KEY WORDS: autoimmune thyroid disease, systemic sclerosis, thyroid cancer, thyroid nodules, thyroid ultrasound

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Autoimmune thyroid disease (AITD) is common in the general population and affects approximately 2–10% of the population worldwide [1]. AITD is a spectrum of diseases that mainly includes Hashimoto's thyroiditis (HT) and Graves' disease (GD), which are the major causes of autoimmune hypothyroidism and hyperthyroidism, respectively [1]. AITD is more common in the presence of another autoimmune diseases and some common pathogenetic pathways have been suggested [2].

Systemic sclerosis (SSc) is a multi-system connective tissue disease that can involve the thyroid gland via an autoimmune mechanism or via scleroderma-related thyroid fibrosis [3]. Several studies have reported a prevalence of AITD in up to 25% patients with SSc [3-8]. However, results to date have been contradictory [2,6,9,10]. There is no known association between AITD and specific clinical or serological subtypes of SSc [6].

Anti-thyroid antibodies–anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG)–are markers of AITD and are positive in up to one-third of SSc patients, more prevalent than in the general population [5-9,11]. Conversely, it has been reported that the lower thyroid volume resulting from fibrosis correlates better with thyroid dysfunction in SSc patients than does antibody status [12]. Timely diagnosis and treatment of thyroid disorders in SSc patients could affect their quality of life [13] as well as pregnancy outcomes [14].

Other autoimmune diseases such as systemic lupus erythematosus (SLE) have an established association with AITD as well as with higher rates of thyroid nodules and cancer [15]. In contrast, thyroid nodules are not considered to be related to scleroderma and data regarding thyroid nodules and cancer in SSc patients are limited.

It has been speculated that thyroid cancer is associated with chronic thyroiditis [16]. Antonelli and colleagues [17] reported a higher prevalence of papillary thyroid cancer in SSc patients, all of whom had thyroid autoimmunity. The researchers concluded that AITD predisposed these patients to papillary thyroid cancer. In addition, patients with SSc have an increased risk of various types of malignancy compared with the general population [18], but the mechanism is yet to be determined.

The goal of this study was to characterize the thyroid gland of patients with SSc biochemically and sonographically and to compare patients with known thyroid disease to thyroid disease naive patients.

PATIENTS AND METHODS

PARTICIPANTS

A total of 50 patients with SSc, followed at the Rheumatology Outpatient Clinic in Meir Medical Center, Israel was consec-

utively recruited to the study. All patients completed the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc [19]. During a routine ambulatory outpatient visit, the patients were interviewed regarding their personal and familial history of thyroid disease and use of thyroid replacement therapy and medications for SSc. Information extracted from the medical records included epidemiological data, clinical characteristics, laboratory results, medications taken, and medical history. Standardized criteria were followed for the definition of organ involvement in SSc. All patients underwent complete laboratory and sonographic evaluations. Patients with known thyroid disease were included.

LABORATORY EVALUATION

Serum thyroid-stimulating hormone (TSH) level determinations and free thyroxine (fT4) were performed using electrochemiluminescence immunoassay, which is intended for use on the Cobas e 801 immunoassay analyzer (Roche, Mannheim, Germany). Normal TSH levels range from 0.23–4 mU/L and normal fT4 levels 0.8–2.0 ng/dl. Anti-TPO and anti-TG were performed using a solid phase, enzyme-labeled, chemiluminescent sequential immunometric assay IMMULITE 2000 (Siemens Healthcare Diagnostics Products, Ltd., Gwynedd, United Kingdom).

Information on SSc-specific autoantibodies-antinuclear (ANA), anti-topoisomerase (Scl-70), and anti-centromere was obtained from the medical records.

ULTRASOUND OF THE NECK AND FINE NEEDLE ASPIRATION (FNA)

Ultrasonographic examination of the thyroid gland was performed by a single expert radiologist (MW) using a Logic9 GE 2005 with L5-12 transducer. The size and texture of the gland were characterized.

The number and size of thyroid nodules were described, as well as their echoic pattern (iso/hyper/hypo-echoic), calcifications (micro- and macro-), and regularity of the borders. For large nodules (≥ 1 cm in diameter) or with features suspicious for malignancy, an ultrasound-guided FNA was performed according to standard clinical practice [20].

STATISTICAL ANALYSIS

Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) depending on their distribution and were compared using Student's *t*-test or the Mann-Whitney test. Normality was assessed using the Shapiro-Wilk test. Categorical variables were compared using chi-square or Fisher's exact test, each as appropriate.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 26 (SPSS, IBM Corp, Armonk, NY, USA). Statistical tests were one-sided or two-sided, depending on the a priori hypothesis, and $P < 0.05$ was considered statistically significant.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Meir Medical Center Ethics Committee (MMC 175-2010). The study was registered at NIH: N CT01270425. All patients signed an informed consent. Patients who underwent aspiration of the thyroid signed a separate informed consent for the procedure.

RESULTS

Fifty patients with SSc were included in the study. The mean age was 51.3 ± 13.5 years and 44 (88%) were women. Table 1 shows the main epidemiological data as well as clinical and laboratory characteristics of SSc in our patients. Overall, 40 patients (80%) had diffuse cutaneous systemic sclerosis and 10 (20%) had limited cutaneous. The median disease duration was 6.5 (3.0–11.5) years (6 years and 7 years in the limited and diffuse subtypes, respectively). The most common clinical

Table 1. General characteristics of patients with systemic sclerosis

Variable	SSc patients, n=50
Age at evaluation (years), mean ± SD	51.3 ± 13.5
Women, n (%)	44 (88)
Diffuse cutaneous systemic sclerosis, n (%)	40 (80)
Duration of SSc (years), median (IQR)	6.5 (3.0–11.5)
Organ involvement, n (%)	
Raynaud's phenomenon	46 (92)
Skin	45 (90)
Gastrointestinal tract	41 (82)
Respiratory	28 (56)
Digital ulcers	26 (52)
Joints	4 (8)
Kidneys	3 (6)
Antinuclear antibodies, n (%)	49 (98)
Anti-topoisomerase (Scl-70) antibodies, n (%)	23 (46)
Anti-centromere antibodies, n (%)	8 (16)
Another autoimmune disease, n (%)	9 (18)
Medical treatment for SSc, n (%)	43 (86)
Calcium channel blockers	6 (12)
Endothelin receptor antagonists	14 (28)
Prostacyclin analogues	13 (26)
ACEI/ARB	7 (14)
Proton pump inhibitors	25 (50)
Immunosuppression	27 (54)

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, SSc = systemic sclerosis

manifestations of SSc were Raynaud's phenomenon and skin fibrosis. Almost all patients had positive ANA (98%), while 46% had anti-topoisomerase (Scl-70) antibodies and 16% had anti-centromere antibodies. Nine patients had an additional autoimmune disease, including four with Sjögren's syndrome and two presented with SLE. Two patients had two or more additional autoimmune diseases. Most of our patients were treated for SSc organ involvement (86%). See details in Table 1. None of our patients were treated with steroids.

Of the 50 patients with SSc, 10 had been previously diagnosed with thyroid disease. Table 2 describes the clinical, biochemical, and sonographic characteristics of the thyroid gland in these patients compared with the 40 patients who were thyroid disease naive.

Among the 50 patients with SSc, 8 (16%) had previously known autoimmune hypothyroidism, 2 underwent hemi-thyroidectomy for unknown reasons, and 7 were treated with thyroid hormone supplements. None of the participants had been exposed to radiation to the neck. One-third of SSc patients had a first-degree relative with autoimmune thyroid disease, predominantly hypothyroidism. Overall, thyroid function test results were within normal limits. There was no statistically significant difference between the two groups, yet thyroid antibodies were noted more frequently in patients with known AITD. Among the thyroid disease naive patients, 3 had borderline elevated TSH levels of 4–5 mIU/l. One of these patients had positive anti-TPO and anti-TG antibodies. Among the patients without known thyroid disease, five (13%) had positive anti-thyroid antibodies (5 were positive for anti-TPO, and 2 were also positive for anti-TG). Three patients of the known thyroid disease group had antibodies for both anti-TG and anti-TPO. In total, 8 (17%) of the SSc patients had anti-thyroid antibodies.

The size of the thyroid gland was normal in 60% in the group with known thyroid disease and 80% in the thyroid disease naive patients. The gland was enlarged in eight patients (seven in the group without a known thyroid disease), while reduced size was measured in four (three with known thyroid disease).

A total of 22 patients (44% of the study population) had 1–6 thyroid nodules. There was no significant difference between the groups in the incidence, size, echoic pattern, or calcifications and regularity of borders of the nodules. At least one nodule > 1 cm was found in 24% of patients. Two nodules were hypoechoic and two had microcalcifications. Overall, six patients underwent ultrasound-guided FNA procedures, four from the group without a known thyroid disease.

Pathological reports were consistent with colloid nodules in five patients and one was diagnosed with papillary thyroid carcinoma after FNA of a nodule with microcalifications. This patient had known autoimmune hypothyroidism without thyroid autoantibodies. Her thyroid gland was small, and she had four nodules, two were > 1 cm.

Table 2. Clinical, biochemical ,and sonographic characteristics of thyroid gland in the study population

Characteristic	All SSc patients N=50	Thyroid disease		*P* value
		Yes N=10	No N=40	
Familial thyroid disease, n (%)	16 (33)	4 (40)	12 (31)	0.420*
Eltroxin treatment, n (%)	7 (14)	7 (70)	0 (0)	< 0.001*
TSH (nl 0.23-4 mIU/L), median (IQR)	2.0 (1.4 - 2.8)	2.3 (1.7 - 3.9)	1.8 (1.3 - 2.8)	0.163
fT4 (nl 0.8-2 ng/dl), median (IQR)	1.0 (0.9 - 1.1)	1.1 (1.0 - 1.1)	1.0 (0.9 - 1.1)	0.381
Anti-TPO antibodies, n (%)	8 (17)	3 (30)	5 (13)	0.207*
Anti-TG antibodies, n (%)	5 (10)	3 (30)	2 (5)	0.054*
Thyroid size, n (%)				
Normal	38 (76)	6 (60)	32 (80)	Low expected counts
Enlarged	8 (16)	1 (10)	7 (17.5)	
Reduced	4 (8)	3 (30)	1 (2.5)	
Thyroid nodules, n (%)	22 (44)	3 (30)	19 (47.5)	0.480**
Thyroid nodules ≥ 1 cm, n (%)	12 (24)	2 (20)	10 (25)	1.000**
Thyroid nodules for FNA, n (%)	6 (12)	2 (20)	4 (10)	0.586**

*one-sided
**two-sided
FNA = fine needle aspiration, fT4 = free thyroxine, IQR = interquartile range, TG = thyroglobulin, TPO = thyroid peroxidase, TSH = thyroid-stimulating hormone

DISCUSSION

AITD has been reported in up to 25% of SSc patients and can occur either via an autoimmune mechanism (HT with lymphocytic infiltration) or via scleroderma-related thyroid fibrosis [3]. Like in previous reports, 16% of patients with SSc in our study had previous diagnosis of AITD, and one-third of SSc patients had a first-degree relative with autoimmune thyroid disease.

We did not detect any new cases of clinically significant AITD. Nevertheless, in the undiagnosed group, three patients had subclinical hypothyroidism and five (13%) had positive anti-thyroid antibodies. Based on previous data, these patients are prone to develop AITD in the future [5,6] and should be monitored periodically. Importantly, it has been reported that more than half of patients with mildly elevated TSH have normal levels in repeated measurements [21]; thus, a single TSH measurement is of limited clinical value. Due to the small sample size, we could not draw conclusions regarding the relation of thyroid disease with a specific clinical or serological subtype of SSc.

Singh et al. [12] prospectively evaluated the thyroid glands of 106 patients with SSc. They reported that the prevalence of thyroid dysfunction was comparable with that of the general population and that the incidence of positive anti-thyroid antibodies was lower than expected (subclinical hypothyroidism in 8.5%, overt hypothyroidism in 1.9%, subclinical hyperthyroidism in 2.8%, overt hyperthyroidism in 0.9%, anti-TPO in 16%, and anti-TSH receptor antibody in 5.7%). Thyroid dysfunction correlated with lower thyroid volume rather than with antibody status. The investigators postulated that decreased thyroid volume and relatively low levels of autoantibodies were due to thyroid fibrosis that led to thyroid dysfunction, and they suggested sonographic screening for these patients.

Interestingly, in our study the size of the thyroid gland was reduced in only four patients, three who had known thyroid disease and only one had anti-thyroid antibodies. Nevertheless, we believe that the relatively low rate of anti-thyroid antibodies in our study is related to thyroid fibrosis, at least in some of the patients. In a systematic study of histologic examinations of thyroid glands from 56 patients with fatal SSc [3], evidence of severe thyroid fibrosis was reported in 14% (versus 2% in an age- and gender-matched control autopsy series). Furthermore, all thyroid glands from the hypothyroid patients were fibrotic, but very few had lymphocytic infiltration. We assumed that patients with SSc are at risk for thyroid dysfunction through both mechanisms and some are found during an autoimmune process leading to gland fibrosis. Another possible explanation to the absence of reduced size of the thyroid gland, suggestive of fibrotic changes, in most of our patients - is the relatively short disease duration and high percentage of patients with diffuse disease. Unfortunately, fibrosis was not assessed by fibro-scan in our study; thus, we could not assess whether some patients with normal-sized glands had signs of fibrosis.

Immunoglobulin 4 (IgG4)-related disease is another fibro-inflammatory disease, characterized by infiltration of IgG4-positive plasmacytes and fibrosis in various organs, including the thyroid gland. Similar to SSc, IgG4-related thyroiditis is possible either due to chronic fibrosis (previously known as Riedel's thyroiditis) or overlap with HT [22].

Thyroid nodules are common in the general population, with prevalence of 19-35% on US and 8-65% on autopsy reports. Nodules are more common in females and older age groups; however, less than 25% of thyroid nodules are > 1 cm [23]. In a large cross-sectional study in Germany, an area of relative iodine deficiency, thyroid nodules were observed on ultrasound scans in 33.1% of the population, and nodules > 1 cm were observed in 11.9% [24].

In our study, ultrasound scans revealed thyroid nodules in almost half of the patients (44%), and half of the patients with nodules (24% of all patients) had nodules > 1 cm. The fact that the prevalence and characteristics of thyroid nodules were similar between patients with known thyroid disease vs. those without, raises the possibility that larger nodules are common in SSc patients, regardless of the presence of AITD. However, over-diagnosis due to screening in our study is also possible.

Six patients in our study underwent ultrasound-guided FNA and one was diagnosed with papillary thyroid cancer.

Information regarding thyroid nodules and thyroid cancer in SSc is sparse. A few cases of thyroid cancer were sporadically reported [4,5,7,18,25] but only one study evaluated the risk of thyroid cancer in SSc patients [17]. Six cases of papillary thyroid cancer were found in the SSc group (1.8%), compared with one case in each control group. All six had either serological or histological evidence of thyroid autoimmunity. Among the SSc patients, 28% had thyroid nodules, compared to controls from iodine-deficient areas but significantly higher than in controls from iodine-sufficient areas (15%). The authors concluded SSc carries an increased risk for papillary thyroid cancer associated with thyroid autoimmunity.

Our patient with thyroid cancer had no evidence of autoimmunity. The increased risk of malignancy in SSc, as well as the immune/fibrotic mechanisms of thyroid dysfunction in these patients may contribute to higher rates of thyroid cancer in SSc patients. Whether SSc by itself carries a higher risk of thyroid cancer remains unclear and should be further explored.

We believe that the relatively high prevalence of large thyroid nodules we reported, as well as the paucity of data about the underlying mechanisms, clinical significance and rates of cancer, strengthen the recommendation to periodically monitor thyroid function in SSc patients with thyroid function and autoantibody tests and sonographic evaluation. Patients with known thyroid nodules or thyroid dysfunction should be monitored more closely. Larger prospective studies are needed to determine the clinical significance of thyroid nodules in SSc.

LIMITATIONS

The limitations of our study were the small sample, the under-representation of patients with limited cutaneous SSc, and the absence of a sex- and age-matched control group regarding sonographic thyroid features and thyroid autoimmunity. Moreover, T3 and TSH-receptor antibody were not measured, and iodine intake was not included in our workup. Another limitation was that we measured thyroid function tests only once and did not follow possible fluctuations over time.

STRENGTHS

The strengths of our study were that it included consecutive SSc patients who were evaluated in the same ultrasound laboratory by the same examiner.

CONCLUSIONS

Biochemical and sonographic evaluation of patients with SSc did not reveal new clinical or autoimmune thyroid disease. Yet, thyroid nodules were common, with a significant proportion of large (> 1 cm) thyroid nodules in patients with diagnosed thyroid disorder, as well as in those who were thyroid disease naive. Their clinical significance remains unclear. Therefore, we recommend routine ultrasound and laboratory evaluations of the thyroid in these patients.

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Few things can help an individual more than to place responsibility on him, and to let him know that you trust him.
Booker T. Washington (1856–1915), American educator, author, orator, and adviser to several presidents of the United States

You can sometimes count every orange on a tree but never all the trees in a single orange.
Attipate Krishnaswami Ramanujan (1929–1993), Indian poet and scholar of Indian literature and Linguistics