Fatigue in patients with systemic sclerosis and hypothyroidism. A review of the literature and report of our experience

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ABSTRACT

Persistent fatigue (defined as ongoing exhaustion, disproportionate to exertion and not adequately alleviated by rest) reduces health-related quality of life of systemic sclerosis (SSc) patients. Fatigue in SSc is associated with reduced capacity to carry out daily activities, work disability and impaired physical function.

Clinical studies demonstrated a high prevalence of autoimmune thyroiditis and hypothyroidism in patients with SSc. Since hypothyroidism and the associated fatigue symptoms could be cured by L-thyroxine (L-T4) substitutive therapy, the evolution of fatigue symptoms in SSc hypothyroid patients treated with substitutive therapy has been recently evaluated, showing an amelioration of the fatigue symptoms.

We have treated 10 clinical hypothyroid and 23 subclinical hypothyroid female SSc patients (all with diffuse scleroderma) with L-T4 substitutive therapy. Mean baseline General Fatigue Index scores in hypothyroid SSc (15.7±5.1) were significantly higher (greater fatigue; p<0.01) than in the same patients after reaching euthyroidism at 4 months (9.6±3.1).

The results suggest that female SSc patients could be screened for thyroid function, overall in presence of fatigue symptoms, and that an appropriate L-T4 substitutive therapy could be useful to mitigate these symptoms.

Further studies are needed in larger samples of hypothyroid patients with SSc to confirm these data. Further longitudinal studies could be also aimed to evaluate if L-T4 therapy could be useful in alleviating complications of SSc (such as skin thickness, pulmonary hypertension, etc.).

Introduction

Systemic sclerosis

Systemic sclerosis (SSc) is characterised by degenerative microvascular phenomena, and immune system activation, that lead to fibrosis of the skin and internal organs (1, 2). Two overlapping SSc forms exist: a) a limited cutaneous scleroderma, that is confined to the skin of face, hands and feet; b) a diffuse cutaneous scleroderma, extended over other areas of the skin, that can involve visceral organs, including kidneys, lungs, heart, and gastrointestinal tract. Patients affected by the limited form show a good prognosis, with a 10-year survival in about 75% of patients, even if about 10% of them develop pulmonary arterial hypertension after 15 years. Patients who present the diffuse form of scleroderma have a 10-year survival of 55%; death is commonly associated with pulmonary, heart and kidney involvement. Patients are usually treated with immunosuppressive drugs, though glucocorticoids have limited application (1, 3, 4).

The diagnosis is established on the basis of clinical suspicion, the presence of autoantibodies (in particular anti-centromere and anti-scl70/anti-topoisomerase antibodies) and only occasionally on biopsy. Regarding the antibodies, 90% of SSc patients have a detectable anti-nuclear antibody; anti-centromere antibody is more common in the limited form (80–90%) compared to the diffuse form (10%), and anti-scl70 is more common in the diffuse scleroderma (30-40%) (5).

The American College of Rheumatology set the diagnostic criteria for scleroderma in 1980 (6).

SSc is associated with significant morbidity (including skin thickening, finger ulcers, joint contractures, pulmonary fibrosis and hypertension, chronic diarrhea, and renal failure) (7).

SSc patients have high rates of symptoms of depression, and SSc is associated with substantially reduced health-related quality of life (HRQoL) (8).

Persistent fatigue (defined as ongoing exhaustion, disproportionate to exertion and not adequately alleviated by rest) reduces HRQoL in SSc patients.

Systemic sclerosis and fatigue

Many studies have addressed the fatigue symptoms in SSc. In a cross-sectional, multicentre study of 659 patients with SSc from the Canadian Scleroderma Research Group Registry, fatigue was assessed during annual visits [with the Short Form 36 (SF-36) health survey vitality subscale]. The mean score of the SSc patients on the SF-36 vitality subscale was 45.6, substantially lower (indicating more fatigue) than for the Canadian general population (65.8). Higher fatigue was significantly associated with the number of medical comorbidities, breathing problems, and the number of gastrointestinal symptoms. Symptoms of depression and pain were also independently associated with fatigue (9).

More recently, among 464 persons with SSc the five highest rated symptoms in terms of frequency and moderate to severe impact on daily activities, respectively, were: fatigue (89 and 72%), Raynaud's phenomenon (86 and 67%), hand stiffness (81 and 59%), joint pain (81 and 64%) and difficulty sleeping (76 and 59%). Fatigue was commonly associated with moderate to severe impact on daily activities (10).

Also, in a Dutch SSc population fatigue was reported to be a bothersome symptom in 92% of patients (11).

In a USA SSc population of 107 scleroderma patients, 76% reported experiencing fatigue and 61% of these patients reported fatigue as one of their three most distressing symptoms (12).

Fatigue ratings by SSc patients are similar to those of patients with other rheumatic diseases, and worse than in the general population (13).

Fatigue in SSc is associated with reduced capacity to carry out daily activities, work disability and impaired physical function (14, 15). Furthermore, in SSc depression and anxiety correlate with local and global disabilities, psychological characteristics and fatigue (16).

The existing studies on fatigue in SSc have been conducted by single-item ratings (10, 11) or measurement scales (including visual analogue scales) (15), the Vitality subscale of the SF-36 (9) and the Multidimensional Assessment of Fatigue scale (12), sometimes with discordant results (17, 18).

The SF-36 Vitality subscale and the Functional Assessment of Chronic Illness Therapy (FACIT) scale are widely used to measure fatigue in SSc patients (19).

A systematic comparison of fatigue levels [evaluated by General Fatigue Index (GFI) of the Multidimensional Fatigue Inventory (MFI-20)] showed the high levels of fatigue reported in SSc were similar to patients with varying types of rheumatic diseases, demonstrating that fatigue warrants greater attention in SSc (13).

Systemic sclerosis and hypothyroidism

The association of systemic autoimmune disorders and thyroid autoimmunity is well known (20, 21).

A high prevalence of hypothyroidism has been shown in patients with SSc by different clinical studies: the prevalence of clinical hypothyroidism ranged from 2.4% to 26%, and that of subclinical hypothyroidism from 3.5% to 26% (22-25).

These findings were confirmed in a recent large group of 202 SSc patients matched with 404 controls, with a similar exposition to iodine deficiency, that demonstrated a significantly higher risk for clinical and subclinical hypothyroidism (with a prevalence of 4% and 17%, respectively) in female SSc patients than in controls (26). Interestingly, mean thyroid stimulating hormone (TSH) value was significantly higher in SSc than in controls, in agreement with other studies (23, 24).

More recently, the incidence of new cases of clinical and subclinical thyroid dysfunction has been studied in a wide group of 179 women with SSc, vs. 179 matched controls, with similar iodine intake (median follow-up 73 months in SSc, vs. 94 months in controls) (27). The study showed a high incidence of new cases of hypothyroidism and thyroid dysfunction in female sclerodermic patients [overall in presence of a border line high (even if in the normal range) TSH, positive anti-thyroperoxidase antibody, hypoechoic and small thyroid], suggesting these patients should have periodically thyroid function follow-up (27).

These results have been recently confirmed in a systematic review and a meta-analysis of literature about studies reporting on prevalence of other autoimmune diseases (AIDs) known to be associated with SSc. The most prevalent associated AIDs were autoimmune thyroid disease (AITD) (10.4%) followed by Sjögren's syndrome (7.7%) and dermatopolymyositis/polymyositis (5.6%) (28).

AITDs have been associated also with clinical features of SSc. In a Japanese study of a total of 210 SSc patients, 30 patients with AITD (14.3%), including 29 with Hashimoto's disease (HT; 13.8%) and one patient with Graves' disease (0.5%) were identified, showing that hypothyroidism was more common among SSc patients with AITD. Patients with AITD were female, had severe facial skin sclerosis and atrophy of the thyroid gland (29).

In a Brasilian study HT was observed in 19.64% of patients with SSc; patients with HT had higher frequency of pulmonary hypertension in relation to patients without HT (66.6% vs. 22.5%) (30).

Autoimmune phenomena are typical of patients with SSc (28), and the association of autoimmune disorders is frequent (31-33), even if its pathogenetic basis is not fully understood. Evidences have been accumulated from animal and human models about the prevalence of a Th1 lymphokine profile in target organs of patients with AITD (34-37), while both Th1 and Th2 activation is present in SSc patients (38-40). It has been postulated that the above mentioned dysregulation of the Th1 immune-response, under the influence of genetic and environmental factors, may involve different organs in the same patient, leading to the appearance of multiple immune-mediated disorders (31, 32, 36).

Hypothyroidism and fatigue

Patients with thyroid diseases show a significant impairment in HRQoL with

Table I. Comparison of thyroid status between female patients with systemic sclerosis (SSc) and hypothyroidism at baseline, and after 4 months of L-T4 therapy.

	SSc before	SSc, 4 months	*p*
n.	33	33	
Age (years)	54 ± 11	54 ± 9	NS
TSH (μIU/mL)	4.1 ± 10.3*	2.1 ± 1.6	0.001
FT4 (pmol/L)	111 ± 5.4	118 ± 6.7	NS
FT3 (pmol/L)	4.4 ± 1.6	4.7 ± 2.2	NS

TSH: thyroid stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine
*=p<0.01 (ANOVA), *vs*. SSc at 4 months.

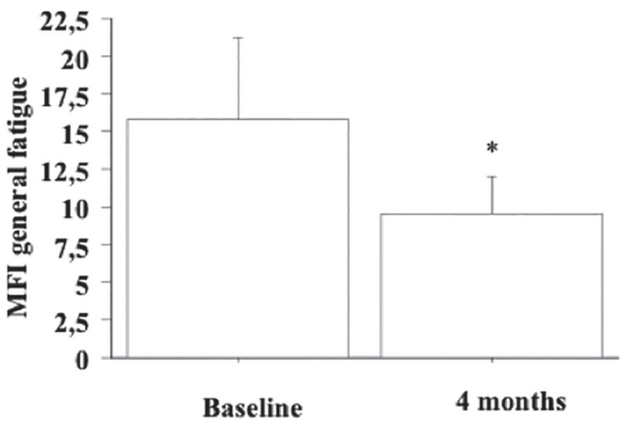

Fig. 1. General Fatigue Index scores for female hypothyroid SSc patients at baseline, and after 4 months of levo-thyroxine substitutive therapy (ANOVA, p<0.01).

respect to the general population (41-43); the reasons of this association are still not clear (42). About one half of patients with thyroid diseases are limited in daily activities and have social and emotional problems, and fatigue.

Patients with untreated thyroid disease suffer from a wide range of symptoms and have major impairment in most areas of HRQoL. For example, 16–51% of hypothyroid patients experience limitations in usual activities during the untreated phase of their disease, and perceive their general health as impaired and have social and emotional impairment. Cognitive problems are also prevalent, as it is fatigue (43).

Fatigue and fatigue-related symptoms are more common in patients with different causes of hypothyroidism. In a cross-sectional study performed in 278 patients [140 patients treated for differentiated thyroid carcinoma (DTC) and 138 with autoimmune hypothyroidism (AIH)] the MFI-20 was used to assess fatigue. AIH patients scored significantly higher than DTC patients in all five MFI-20 subscales, suggesting that AIH patients had significantly higher levels of fatigue compared with DTC patients (44).

In thyroidectomised patients with thyroid cancer a prospective longitudinal cohort study was conducted evaluating the FACIT-Fatigue (FACIT-F) questionnaire for detecting hypothyroid symptoms, after thyroxine withdrawal. FACIT-F correlated with TSH, but was not sensitive to detect mild hypothyroidism (45). Also other studies had similar results (46, 47).

Women with HT suffer from a high symptom load and fatigue, and hypothyroidism is only a contributing factor to the development of associated conditions (48, 49).

However, other studies determined whether subclinical hypothyroidism causes decrements in health status, mood, and/or cognitive function. In a double-blinded, randomised, crossover study of usual dose L-thyroxine (L-T4) (euthyroid arm) vs. lower dose L-T4 (subclinical hypothyroid arm) in hypothyroid subjects, quality of life was evaluated (50). Measures of working memory (N-back, subject ordered pointing) were worse during the subclinical hypothyroid arm, showing mild decrements in health status and mood in L-T4-treated hypothyroid subjects when subclinical hypothyroidism was induced in a blinded, randomised fashion (50).

Studies have been conducted also to evaluate the impact of the therapy with thyroxine-triiodothyronine combination therapy *versus* thyroxine monotherapy for clinical hypothyroidism, with discordant results (51, 52).

Autoimmune thyroiditis, hypothyroidism, and fatigue in SSc patients: a report of our experience

Since clinical studies demonstrated a high prevalence of hypothyroidism in patients with SSc (clinical hypothyroidism ranged from 2.4% to 26%, while that of subclinical hypothyroidism ranged from 3.5% to 26%), and since hypothyroidism and the associated fatigue symptoms could be cured (at least in part) by L-T4 substitutive therapy, we have recently evaluated the evolution of fatigue symptoms in SSc hypothyroid patients treated with substitutive therapy.

All patients gave informed consent to the study, which was approved by the Institutional Ethics Committee. All patients were submitted to thyroid ultrasound, as previously reported (26), showing the presence of autoimmune thyroiditis in all patients. All patients had haemoglobin within the normal range from 11.5 to 14 g/dL. Patients were not affected by other clinical conditions that may explain fatigue such as lung or heart disease.

We have treated 10 clinical hypothyroid and 23 subclinical hypothyroid female SSc patients (all with diffuse scleroderma) (mean age 54±11) with L-T4 substitutive therapy. A first control of TSH, free triiodothyronine (FT3), free thyroxine (FT4) was made after 2 months, the dosage of the therapy was adjusted, and patients were re-evaluated at 4 months (see Table I).

SSc patients completed the GFI of the MFI-20 at baseline, and at 4 months (13). Mean baseline GFI scores in hypothyroid SSc (15.7±5.1) were significantly higher (greater fatigue; ANOVA, p<0.01) than in the same patients after reaching euthyroidism at 4 months (9.6±3.1) (Fig. 1), suggesting that the fatigue symptoms could be mitigated, even if not completely cured, by L-T4

therapy in hypothyroid SSc patients. Changes of GFI scores correlated ($p<0.01$) with TSH, but not with other clinical or immunological parameters in these SSc patients.

Conclusion

Persistent fatigue (defined as ongoing exhaustion, disproportionate to exertion and not adequately alleviated by rest) reduces HRQoL of SSc patients. Fatigue in SSc is associated with reduced capacity to carry out daily activities, work disability and impaired physical function. Since clinical studies demonstrated a high prevalence of hypothyroidism in patients with SSc, and since hypothyroidism and the associated fatigue symptoms could be cured by L-T4 substitutive therapy, we have recently evaluated the evolution of fatigue symptoms in SSc hypothyroid patients treated with substitutive therapy, showing an amelioration of the fatigue symptoms.

These results suggest that female SSc patients could be screened for thyroid function, overall in presence of fatigue symptoms, and that an appropriate L-T4 substitutive therapy could be useful to mitigate these symptoms. However, further studies are needed in larger samples of hypothyroid patients with SSc to confirm these data. Further longitudinal studies could be also aimed at evaluating if L-T4 therapy could be useful in alleviating complications of SSc (such as skin thickness, pulmonary hypertension, etc.).

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