

Thyroid disorders, hyperprolactinemia and systemic lupus erythematosus activity

Aim: The aim of this study was to determine the relationship between thyroid disorders and prolactin in patients with and without lupus activity. **Patients & methods:** Women with systemic lupus erythematosus (SLE) were evaluated for lupus activity. Serum tri-iodothyronine (T_3), serum thyroxine (T_4) and thyroid-stimulating hormone (TSH), anti-thyroid peroxidase (anti-TPO) anti-thyroglobulin (anti-TG) and prolactin were measured. **Results:** 50 women with SLE with lupus activity and 50 women with SLE without activity with mean age of 34.5 ± 14.8 years and mean disease duration of 15.0 ± 2.8 years. Patients with disease activity, subclinical hypothyroidism, anti-TG and anti-TPO were more prevalent and had higher prolactin levels compared with those without disease activity. There was no difference in prolactin levels according to the presence of hypothyroidism, and antithyroid antibody positivity did not differ in patients with and without hyperprolactinemia. **Conclusion:** There was no relationship between thyroid dysfunction, including antithyroid antibodies, with hyperprolactinemia in patients with lupus activity.

Keywords: antithyroid antibodies • disease activity • hyperprolactinemia • subclinical hypothyroidism • systemic lupus erythematosus

Background

The immune–neuroendocrine system participates in the pathogenesis and clinical expression of autoimmune rheumatic diseases. During inflammatory stimulation and active disease, the interaction between the hypothalamic–pituitary–adrenal, hypothalamic–pituitary gonadal, hypothalamic–pituitary–thyroid, and prolactin (PRL) axes with the immune system is evident. Therefore, the abnormal response of the immune–neuroendocrine system may participate in breaking immune cell tolerance [1,2].

Chronic autoimmune thyroiditis or Hashimoto's thyroiditis is an organ-specific autoimmune disease characterized by the presence in serum of autoantibodies against thyroglobulin (Anti-Tg Abs) and thyroid peroxidase (Anti-TPO Abs) and clinical evidence of goiter or atrophic glands [3]. Its relationship with rheumatic diseases, such as SLE, Sjogren's syndrome (SS), systemic sclerosis (SSc) or

rheumatoid arthritis (RA) is well recognized [3–7]. A recent study found a prevalence of thyroid dysfunction of 36%, of which 50% were autoimmune in nature (positive autoantibodies) and a significant association between disease activity and thyroid dysfunction [3]. Thyroid disorders are frequent in SLE and are multifactorial, with a higher prevalence of hypothyroidism and thyroid autoantibodies.

On the other hand, mild-to-moderate hyperprolactinemia (HPRL) has been demonstrated in 15–33% of SLE patients of both genders [8]. In 66% of SLE patients, the causes are unknown and it is classified as idiopathic HPRL [9]. Human studies have suggested that high levels of PRL are associated with SLE activity, major and minor organ involvement such as joint and cutaneous manifestations, nephritis, and neuropsychiatric involvement [10].

However, the relationship between thyroid and PRL disorders in SLE patients has

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not been completely elucidated. In the 1970s, Snyder *et al.* showed that changes in normal serum levels of T_3 and T_4 are associated with changes in PRL responses to the thyrotropin-releasing hormone (TRH); subnormal serum levels of T_3 or T_4 increase TRH-induced PRL release, whereas higher than normal serum levels of T_3 and T_4 inhibit this release [11]. Thus, hypothyroidism has been considered as a secondary cause of HPRL. PRL also has a potential permissive factor in thyroid autoimmunity, with a greater prevalence of antithyroid antibodies being observed in patients with HPRL [12].

However, the interaction between thyroid hormones and PRL has not been analyzed in SLE patients according to their disease activity. Therefore, the aim of this study was to compare thyroid and prolactin hormones, and anti-thyroid antibodies in SLE patients with and without lupus activity.

Patients & methods

Patients

We made a cross-sectional study of female SLE patients attended by the Systemic Autoimmune Disease Research Unit of the Hospital General Regional No. 36 IMSS and Laboratorios Clínicos de Puebla, Mexico. All patients satisfying the American College of Rheumatology revised criteria for SLE classification [13] were consecutively selected and assessed for SLE disease activity. Patients aged ≥ 18 years were included. Exclusion criteria were pregnancy, pituitary adenomas, previously diagnosed hypothyroidism, renal failure, hepatic disorders and high prolactin levels associated with drugs. The local ethics committee approved the study and all patients provided written informed consent to participate in the study.

Methods

Disease activity was scored using the Systemic Lupus Erythematosus Disease Activity Index validated for the Mexican population (mexSLEDAI) [14]. A mexSLEDAI score ≥ 2 was considered as active disease. Therefore, the values of thyroid function, anti-thyroid antibodies and PRL in the sera of patients with mexSLEDAI score of ≥ 2 were compared with the results obtained in patients with a mexSLEDAI score of < 2 .

Thyroid assessment

In clinical evaluation, serum samples of patients were taken during the morning (8 am- 10 am) in fasting state and kept frozen until the laboratory assay was performed. Serum T_4 (thyroxine), FT_4 (free thyroxine), T_3 (triiodothyronine), FT_3 (free triiodothyronine) and TSH (thyroid-stimulating hormone) were determined in all patients by chemiluminescence using ARCHITECT i2000 (SR) immunoassay analyzer (Abbott Diagnostics).

The normal range for TSH is 0.3 to 4.94 μ U/ml, and for FT_3 and FT_4 the ranges are 1.71 to 3.71 pg/ml and 0.7 to 1.48 ng/dl, respectively. We analyzed anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) using chemiluminescence (ARCHITECT plus, Abbott Diagnostics, IL, USA). Serum anti-TG levels above 3 U/ml were considered positive, and anti-TPO levels above 2 U/ml were considered positive.

Clinical hypothyroidism was defined as elevated TSH and suppressed FT_4 , while subclinical hypothyroidism was defined as elevated TSH with a normal FT_4 . Patients with suppressed TSH levels with normal FT_4 levels were considered as subclinical hyperthyroidism. Patients with suppressed TSH and elevated FT_4 levels were defined as clinical hyperthyroidism. Euthyroid sick syndrome (ESS) was defined as low total T_3 .

Prolactin determination

All baseline samples were taken at 8–10 am during fasting. Serum prolactin levels were measured by immunoradiometric assay (Abbott, ARCHITECT i2000 SR). Normal PRL levels are 2–20 ng/ml. HPRL was defined as > 20 ng/ml and mild HPRL as > 20 –40 ng/ml [9].

Statistical analysis

Descriptive statistics including the mean, median and standard deviation (SD) for each continuous variable and frequencies for each categorical variable were tabulated. Two-sample *t*-tests were used to show differences between groups in continuous variables and the chi-square test was used to assess differences between groups in the prevalence of the parameters evaluated. Logistic regression analysis was performed to determine associations between thyroid hormone levels, PRL levels and antithyroid antibodies in patients with and without lupus activity. A *p*-value < 0.05 was considered statistically significant in the multivariate analysis. The analysis was made using SPSS software version 17.0 for Windows.

Results

50 women with SLE with disease activity and 50 women without disease activity were included. Demographic and clinical data are summarized in Table 1. The mean age was 39.0 ± 10.3 in patients with disease activity and 43.0 ± 12 years in those without (non-significant). The disease duration was 9.5 ± 7.2 years in patients with disease activity and 10.5 ± 8.4 years in those without (*p* = 0.5). Disease activity measured by the mexSLEDAI was 3.9 ± 2.4 in patients with disease activity.

Thyroid assessment

The results of the thyroid function tests are described in Table 1. 9% of patients had subclinical hypothy-

Table 1. Demographic, clinical and laboratory findings characteristics of systemic lupus erythematosus patients.

Variable	All SLE patients (n = 100)
Age, mean ± SD, years	34.5 ± 14.8
SLE duration disease, years	15 ± 2.8
SLE activity (%)	50 (50.0)
Prednisone (%)	95 (95.0)
Prednisone daily dose mg, mean ± SD	10.54 ± 6.5
Antimalarials (%)	68 (68.0)
Immunosuppressive therapy (%)	48 (48.0)
PRL ng/ml, mean ± SD	21.6 ± 17.9
FT ₃ pg/ml, mean ± SD	2.7 ± 0.5
T ₃ ng/dl, mean ± SD	1.0 ± 0.2
FT ₄ ng/dl, mean ± SD	1.1 ± 0.8
T ₄ ng/dl, mean ± SD	7.9 ± 2.3
TSH μU/ml, mean ± SD	2.8 ± 1.6
Anti-TPO AB positive (%)	17 (17.0)
Anti-TG AB positive (%)	20 (20.0)

Anti-TG AB: Anti-thyroglobulin antibodies; Anti-TPO AB: Anti-thyroid peroxidase antibodies; FT₃: Free triiodothyronine; FT₄: Free thyroxine; Mex-SLEDAI: Systemic lupus erythematosus disease activity index; PRL: Prolactin; SLE: Systemic lupus erythematosus; T₃: Thyroxine; T₄: Thyroxine; TSH: Thyroid-stimulating hormone.

roidism and only one patient had subclinical hyperthyroidism. ESS was also present in only one patient. 30 patients had at least one antithyroid antibody. Both antithyroglobulin and anti-thyroid peroxidase antibodies were detected: seven patients had anti-TG only, 11 patients had anti-TPO only and 12 had both. Eight (66.7%) of the thyroid dysfunctions were autoimmune (positive autoantibodies) and four (33.3%) were non-autoimmune. 53 (60.2%) patients had normal thyroid function with positive autoantibodies.

Prolactin determination

Mean serum total prolactin was 21.6 ± 17.9 ng/ml. Normal prolactin levels were found in 62% of patients, HPRL in 38% and mild HPRL in 31% of patients.

Thyroid assessment & lupus activity

Table 2 shows the results of the thyroid assessment in patients with and without lupus activity. TSH levels in patients with and without disease activity were 3.6 ± 1.63 μU/ml and 2.1 ± 0.3 μU/ml, respectively (p = 0.005). There were no significant differences in T₃, FT₃, T₄ and FT₄ levels between groups. Patients with active disease have a higher prevalence of hypothyroidism (18.0 vs 0%; p = 0.001). Patients with disease activity had a higher prevalence of anti-TG and anti-TPO compared with those without. When the prednisone daily dose, antimalarials and immunosuppressives therapies were compared in patients with

and without thyroid abnormalities, there were no significant differences.

PRL determination & lupus activity

PRL levels were significantly higher in patients with disease activity compared with those without (25.3 ± 14.9 vs 17.9 ± 4.8 ng/ml) (Table 2). However, there was no relationship between both variables when Spearman correlation was performed (r = 0.17; p = 0.9). Also, when treatment characteristics were compared between patients with and without HPRL, any significant differences was found.

Thyroid assessment & PRL determination

There was no difference in PRL levels according to the presence or not of hypothyroidism (26.3 ± 11.7 vs 20.9 ± 18.6 ng/ml, respectively; p = 0.39), even in the active disease group (26.3 ± 11.7 ng/ml vs 25.1 ± 19.9 ng/ml, respectively; p = 0.85). Antithyroid antibody positivity did not differ in patients with or without HPRL (45 vs 46%; p = 0.5).

Logistic regression analysis

Finally, a logistic regression analysis was made in order to measure all variables considering the presence of antithyroid antibodies in the SLE patients with and without disease activity. A statistically significant difference was found in the variables included. In patients with disease activity, a higher ratio Exp (B) in the three

Table 2. Thyroid function and serology in systemic lupus erythematosus patients with and with disease activity.

Variable	With activity (n = 50)	Without activity (n = 50)	p-value
Thyroid function, mean (SD)			
TSH μ U/ml	3.63 (1.6)	2.15 (0.3)	0.01
FT ₃ pg/ml	2.6 (0.4)	2.7 (0.6)	0.56
FT ₄ ng/dl	1.2 (1.1)	1.0 (0.1)	0.11
Serology (%)			
Anti-TPO AB positive	40.0	6.0	0.005
Anti-TG AB positive	32.0	6.0	0.009
Prolactin, ng/ml, mean (SD)	25.3 (14.9)	17.9 (4.8)	0.04

Anti-TG AB: Anti-thyroglobulin antibodies; Anti-TPO AB: Anti-thyroid peroxidase antibodies; FT₃: Free triiodothyronine; FT₄: Free thyroxina; TSH: Thyroid-stimulating hormone.

variables (TSH, anti-TPO, anti-TG) included in the model was found (Table 3).

Discussion

This study investigated the interaction between thyroid function and prolactin in patients with SLE. We found that patients with active SLE (mexSLEDAI score ≥ 2) had a greater prevalence of thyroid dysfunction, mainly hypothyroidism, anti-TG and anti-TPO antibodies and HPRL levels, compared with patients with inactive disease.

SLE is a complex disease with multisystemic involvement, which presents with periods of remission and exacerbation. This multisystemic involvement can also affect the endocrine system, with a higher prevalence of antithyroid autoantibodies compared with the general population [3,15], mainly in relation to hypothyroidism. We found that 11% of SLE patients had thyroid dysfunction and 9% had subclinical hypothyroidism, it was similar to other reports [16,17]. However, there are some differences with a recent Chinese study, the authors found that the prevalence of autoimmune thyroid disease was 2.78%, clinical hypothyroidism 1.69%, subclinical hypothyroidism 10.04%, central hypothyroidism 1.29%, hyperthyroidism 1.19%, euthyroid sick syndrome (ESS) 9.54%, and

nodules 1.09%, respectively [18]. This may be partially explained by ethnic differences [18] and severity of lupus [19], which could influence autoantibody positivity.

The prevalence of antithyroid antibodies was 30%, similar to the figures found by other studies [20,21]. Patients with active disease measured by the mexSLEDAI had a higher prevalence of positive antithyroid antibodies compared with those without activity. 30 patients had at least one antithyroid antibody and 12 had both, all with disease activity. Magaro *et al.* found that 45.5% of patients with active SLE presented antithyroid antibodies and that anti-thyroglobulin and anti-microsomal antibodies were not found in any patient with inactive SLE or in controls [21]. However, we found positive antithyroid antibodies (both anti-TPO and anti-TG) in a few patients without lupus activity. In contrast, Mader *et al.* found no correlation between antithyroid antibodies levels and the degree of disease activity (SLEDAI score ≥ 6). Disease activity was measured in our patients using another instrument and a different score. In addition, autoantibodies may fluctuate over time [22].

Previously reported frequencies of HPRL in SLE patients have ranged from 2 to 37.5% [23,24]. We found that SLE women with disease activity had significantly higher prolactin levels than those without, although

Table 3. Relationship between disease activity and thyroid-stimulating hormone, antithyroid antibodies and prolactin[†].

Variable	β	Exp (B)	p-value
TSH	1.15	3.1	0.01
Anti-TPO AB	2.2	11.6	0.01
Anti-TG AB	2.13	8.1	0.02
Prolactin	0.03	1.0	0.02

[†]Logistic regression analysis, forward conditional method; p < 0.05 was considered significant. Anti-TG AB: Anti-thyroglobulin antibodies; Anti-TPO AB: Anti-thyroid peroxidase antibodies; Exp (B): Odds ratio; TSH: Thyroid-stimulating hormone.

the possible relationship between lupus activity and prolactin disappeared when bivariate exploration using correlation analysis was performed. This finding might be due to most of our patients had mild or moderate disease activity with few patients with severe activity. Our findings are similar to those of other studies. Pazuener *et al.* found that HPRL is likely not associated with disease activity in SLE [25]. Buskila *et al.* found no correlation between prolactin levels and clinical activity in patients with SLE [26] as did Jimena *et al.* [27]. However, several studies show opposing results [9,28–30]. The differences may be due to the study design, observational bias or the effects of medication.

Unlike other studies, we found no correlation between thyroid disorders, including positive antithyroid antibodies, and HPRL. Ferrari *et al.* were the first to describe thyroid autoimmunity in HPRL disorders [12]. Subsequently, Kramer *et al.* investigated possible relationships between HPRL and markers of thyroid autoimmunity in patients with SLE and rheumatoid arthritis and found that the PRL level was higher in SLE patients and an increased prevalence of antithyroid antibodies in patients with HPRL, demonstrating an association between prolactin and autoimmunity [31].

The role of PRL in the interrelation between the endocrine and immune systems has been evaluated in several studies. PRL is produced by several hematopoietic cells and exerts a cytokine-like activity through specific receptors expressed in the immune system cells. This issue has been treated in a recent review [32].

Another situation in which PRL has potential permissive factor is thyroid autoimmunity, with a greater prevalence of antithyroid antibodies observed in patients with HPRL [12]. Hypothyroidism can lead to HPRL as mentioned previously [12]. On the other hand, HPRL has been associated not only with lupus activity but also with positivity for various autoantibodies (anti-DNA, ANA and antithyroid antibodies), as part of the potential impact of autoimmunity [31]. Surprisingly, our study failed to find any relationship between PRL levels and antithyroid antibodies prevalence.

Our study has several limitations. First, antithyroid antibody determinations were performed qualitatively and not quantitatively, which is more accurate. Second, the cross-sectional nature of the study did not allow consideration of changes over time in lupus activity and thyroid disorders. Third, although the sample size was statistically adequate, studies with a larger sample would be necessary to confirm our findings.

Conclusion & future perspective

In conclusion, SLE women have endocrine disorders such as thyroid dysfunction and positive antithyroid antibodies. Although, there was a slight trend to higher levels of prolactin in patients with disease activity measured by the mexSLEDAI, this was not confirmed by correlation analysis. One third of the patients had antithyroid antibodies, which were more prevalent in patients with lupus activity. There was no relationship between thyroid dysfunction, including antithyroid

Executive summary

Background

- The aim of this study was to evaluate possible relationships between thyroid dysfunction, antithyroid antibodies and prolactin in patients with and without lupus activity.

Patients & methods

- A cross-sectional study was performed in women with systemic lupus erythematosus (SLE): two groups were studied according to lupus activity measured by the mexSLEDAI score (≥ 2). Thyroid hormones were measured: serum tri-iodothyronine (T_3), serum thyroxine (T_4) and thyroid-stimulating hormone (TSH), as well as antithyroid peroxidase (anti-TPO) anti-thyroglobulin (anti-TG) and prolactin.

Results

- 50 women with SLE with lupus activity and 50 women with SLE without activity with a mean age of 34.5 ± 14.8 years and a mean disease duration 15 ± 2.8 years. TSH levels were lower in patients with disease activity. Subclinical hypothyroidism was the most-frequent thyroid disorder and was more prevalent in patients with lupus activity compared with those without (18.0 vs 0%; $p = 0.001$). Patients with disease activity had a higher prevalence of anti-TG and anti-TPO than those without (40.9 vs 6.0%; $p = 0.005$ and 32.0 vs 6.0%; $p = 0.009$, respectively). Prolactin levels were significantly higher in patients with disease activity compared with those without ($25.3 \text{ ng/ml} \pm 14.9$ vs $17.9 \text{ ng/ml} \pm 4.8$; $p = 0.04$). There was no difference in prolactin levels according to the presence of hypothyroidism, and antithyroid antibody positivity did not differ in patients with and without hyperprolactinemia (45 vs 46%; $p = 0.5$).

Conclusion

- Women with SLE thyroid dysfunction, positive antithyroid antibodies and hyperprolactinemia were frequent, predominantly in patients with lupus activity. There was no relationship between thyroid dysfunction, including antithyroid antibody and hyperprolactinemia. This lack of relationship was also found in active patients.

antibody positivity in patients with HRPL. This lack of relationship was also found in active patients. Larger, longitudinal studies may elucidate this possible relationship.

The role of dopamine agonists in treatment of autoimmune diseases is yet to be determined. The genetic factor and the role of the different prolactin isoforms in the pathogenesis and activity of autoimmune diseases are not clear yet.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or

materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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