Review of major endocrine abnormalities in patients with systemic lupus erythematosus

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Abstract

Objective

Systemic lupus erythematosus is associated with an increased risk of developing an endocrine disease. These endocrinopathies can closely mimic SLE symptoms ranging from fatigue to renal involvement but the treatment is often very different.

Methods

A careful review of the PubMed and MEsH databases linking endocrine disease to SLE was performed. A retrospective analysis of the 708 SLE patient cohort at University College London Hospital (UCLH) has been completed. They have been followed for at least one year from 1978 to 2017. In our study, we report how often these endocrine diseases are identified in lupus patients compared to the general population and whether these patients with both diseases had a poorer prognosis. We have attempted to establish if the endocrine diseases develop before or after the lupus diagnosis.

Results

The literature search produced some conflicting results. 708 SLE patients were included in our study. We found 67 endocrine diseases in 55 different patients of our cohort. The most common endocrinopathy was hypothyroidism (5.22%) followed by type 2 diabetes mellitus (1.41%) and hyperthyroidism (1.41%). Other endocrine disorders also identified were type 1 diabetes mellitus (0.42%) and hyperparathyroidism (0.70%). In terms of mortality, lupus patients with concomitant endocrine disease had similar outcomes compared to those without endocrine disease (16.36% died vs. 15.16%). In general terms, these endocrine diseases were developed after the lupus diagnosis. We found that the 21.8% of our SLE plus endocrinopathy patients also have an increased risk of developing a second endocrine disease.

Conclusion

We report concomitant endocrine disease in 7.76 % of our 708 SLE cohort followed, for almost 40 years, at UCLH. These patients have increased liability to develop a second endocrine disease, but overall there is no difference in terms of mortality between SLE patients with or without an endocrinopathy. It is important to capture endocrine diseases in SLE as the symptoms they cause may mimic SLE features, but require quite distinct treatment.

Key words

systemic lupus erythematosus, hypothyroidism, hyperthyroidism, diabetes mellitus, hyperparathyroidism, hypothyroidism, Addison's disease

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disorder characterised by many clinical manifestations often involving several organs and systems. Thus patients have a variable prognosis and often experience a reduced quality of life.

Patients with SLE may also develop a range of endocrine diseases, such as hypothyroidism, hyperthyroidism or Addison's disease (8, 29-30). Given that endocrine diseases may cause symptoms ranging from fatigue to severe renal impairment that can mimic features of SLE, it is clearly important to diagnose them quickly and treat them appropriately.

Different international studies have ed the prevalence of endocrine diseases in SLE patients compared with the normal population and they vary considerably. In this review, we have analysed the literature linking endocrine diseases with SLE. We have focused on: hypothyroidism, hyperthyroidism, type I diabetes mellitus (T1DM) and type II diabetes mellitus (T2DM), hyperparathyroidism, hypoparathyroidism and Addison's disease.

We reviewed the prevalence of these endocrinopathies in SLE patients noting ranges of: hyperthyroidism: 0–5.19% [1-4, 6, 11-15, 32); hypothyroidism: 2.7–21.5% (1-6, 11-19, 32) and diabetes mellitus (DM): 1.85–3.3% (7, 10, 11, 31). Most studies observed an increased prevalence of hypothyroidism (1-6, 11-19, 32) in SLE patients, compared to the normal population. With regard to hyperthyroidism (1-4, 6, 11-15, 32) and T1DM/T2DM (7, 10, 11, 31), different results have been reported. A few case reports of Addison's disease in SLE patients have been published and no prevalence study is available to date.

In addition, we carefully reviewed the occurrence of endocrine diseases identified among the 708 patients followed up at University College Hospital (UCLH) from 1978 to 2017. We also considered the temporal relationship between the onset of SLE and the various endocrine diseases. We wondered whether those patients with endocrine diseases were more likely to have a second endocrine disease. Finally, we sought to determine whether those patients with concomitant endocrine disease have a poorer prognosis.

Materials and methods

We carefully reviewed the world literature linking lupus and endocrine diseases in the main databases (PUBMED, MEsH). The terms used for the search were: "lupus and hypothyroidism", "lupus and hyperthyroidism", "lupus and diabetes mellitus", "lupus and hyperparathyroidism", "lupus and hypoparathyroidism", "lupus and Addison's disease".

We reviewed around 80 publications including studies, reviews and case reports in two languages (Spanish (10, 24, 28) and English). These studies ranged from October 1987 to November 2017.

A retrospective analysis was completed using the UCLH SLE patient database for this report. We have extracted data from our 708 SLE patients, all whom have fulfilled the revised American College of Rheumatology (ACR) SLE classification criteria (9). They were regularly reviewed at the UCLH from 1978 to 2017 and completed a minimum of one year of follow-up. Data on the development of endocrine disease in our lupus cohort was collected prospectively from 1978. To make sure we were not missing any endocrine diseases we undertook a very detailed review of a random selection of cases (not known to have endocrine problems) to ensure we were not missing any key data. Among our SLE cohort, the 91.6% (649) were women and the 8.3% (59) were men.

We attempted to establish if endocrine diseases develop before or after the SLE diagnosis. We also reviewed the hospital notes from rheumatology and endocrinology during the follow-up period.

In addition, we checked the different blood test parameters which are characteristic of these diseases (TSH, T4, glycaemia, glycated haemoglobin, anti-thyroid antibodies [microsomal, thyroglobulin and thyroid hormone anti-receptor autoantibodies] cortisol, vitamin D and ACTH).

Results

Patient characteristics

All 708 SLE patients in the UCLH cohort were included in this study.

We identified 67 endocrine diseases (Table I) in 55 different patients (7.76% of the total lupus cohort). Our detailed review of 100 patients not recorded as having endocrine diseases reassured us as no 'unexpected' conditions were identified. The diagnoses were invariably confirmed by an endocrinologist. Furthermore, 21.8% of those with one endocrine disorder had more than one of these conditions. Representative prevalence studies showing the extreme among the cohort reported are shown in Table II.

Table I. Summary of major endocrine diseases in our UCLH SLE cohort.

	Hypothyroidism	Hyperthyroidism	Diabetes Mellitus	Hyperparathyroidism
Percentage of endocrine diseases in the UCLH cohort	5.22% (37/708)	1.41% (10/708)	1.83% (13/708)	0.70% (5/708)
Mean age at onset (in years)	39.6	34.7	41.3	41.6
Sex	Woman: 91.89% Men: 8.11%	Woman: 90% Men: 10%	Woman: 92.3% Men: 7.7%	Woman: 80% Men: 20%

Table II. Representative prevalence studies of concomitant endocrine disease in lupus patients.

References	Number of patients	Hypothyroidism	Hyperthyroidism	Diabetes Mellitus
Ong SG *et al*.[2]	189	3.7%	2.6%	—
Pyne *et al*.[4]	300	5.7%	1.7%	—
Molina *et al*.[11]	877	19%	0.3%	—
Domingues SL *et al*.[13]	79	21.5%	3.9%	—
Watad A *et al*.[1]	5018	15.58%	2.59%	—
Chan AT *et al*. [14]	69	17.4%	5.8%	—
Antonelli A *et al*.[6]	213	5.9%	1.5%	
Cortes S *et al*.[7]	485	—	—	1.85%
Gallego C *et al*.[10]	304	—	—	3.3%

SLE and hypothyroidism

We found a total of 37 SLE patients with clinical hypothyroidism (5.22% of the total in the UCLH SLE cohort). Among these patients, 16 had one or more of the thyroid antibodies tested positive. 11 of them had negative thyroid antibodies and in 10 cases we could not identify the results.

We determined whether hypothyroidism was more likely to appear after or before the SLE diagnosis. In 17 patients, the hypothyroidism appeared later [range: 3–35 years; mean: 12 years; median: 9 years]. In 11 patients, the hypothyroidism appeared before [range: 1–12 years, mean: 5.45 years; median: 4 years]. In 9 cases we had insufficient data to be certain.

In addition, we have observed that 12 of these 37 patients with hypothyroidism have a second endocrine disease, the most common being the T2DM (6) but others included hyperparathyroidism (2), T1DM (1), hypoparathyroidism (1) and panhypopituitarism (1).

SLE and hyperthyroidism

We identified 10 patients with clinical hyperthyroidism (1.41% of the total of the UCLH SLE cohort). Among these patients, we found, eight (80% of the total), had positive anti-thyroid antibodies one had no anti-thyroid antibodies and in one patient we could not find a record of the antibody results.

Analysing the temporal relationship between SLE and endocrine disease, the endocrine disorder appeared later than SLE in six patients [range: 2–17 years; mean: 8.6 years; median: 7 years]. In four cases, it appeared before [range: 2–26 years; mean: 17.25 years; median: 20.5 years]. One patient with hyperthyroidism had another endocrine disease (secondary hyperparathyroidism).

SLE and type 1 diabetes mellitus

We found three patients with T1DM1 (0.42% of the total of our SLE cohort). Each developed their endocrine disease before the SLE [range: 11–29 years, mean: 20 years; median: 20 years]. One of them had a second endocrine disease (hypothyroidism).

SLE and type 2 diabetes mellitus

We identified 10 patients with T2DM (1.41% of the total of our SLE cohort) with a range between 32 and 64 years old.

In nine of these patients, the endocrine disease developed after SLE was diagnosed [range: 3 months to 24 years; mean: 12.9 years; median: 8.5 years]. In one patient, the DM developed subsequently. In five patients, the T2DM was steroid-induced, four had a spontaneous T2DM and in one patient, there were insufficient data to be certain. 50% of these patients had a second endocrine disease (each with hypothyroidism).

SLE and hyperparathyroidism

We found five patients who also had hyperparathyroidism which equals 0.70% of our SLE cohort.

The hyperparathyroidism appeared later than the SLE in all patients [range: 11–34 years; mean: 23 years; median: 29 years]. One patient (0.14%) had a primary hyperparathyroidism due to parathyroid adenoma and the other four patients (0.56%) had secondary hyperparathyroidism due to a chronic renal failure as a result of lupus nephritis. Two of the SLE patients who had hyperparathyroidism also had hypothyroidism. One of them had hyperthyroidism as a second endocrine disease.

SLE and other endocrine diseases

None of our SLE patients was diagnosed with Addison's disease. In contrast, other endocrine diseases were found in two patients; one with a panhypopituitarism, the other with hypoparathyroidism associated with hypothyroidism (both of these diseases developed later than the SLE).

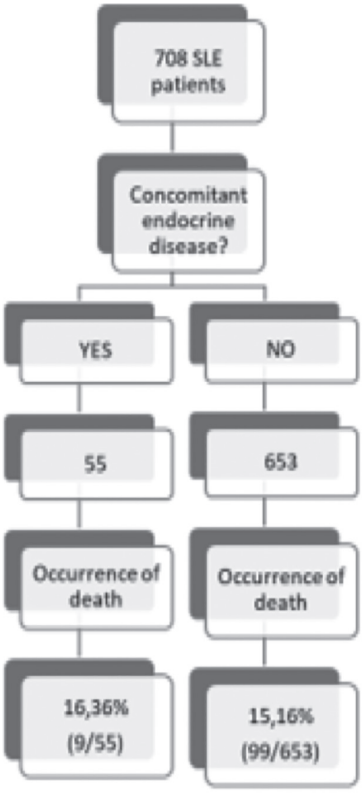

Fig. 1. Occurrence of death in SLE patients with and without endocrine disease.

Prognosis in terms of deaths comparing SLE patients with and without endocrine disease

108 of the patients in our 708 SLE cohort (15.25%) died during the follow-up of almost 40 years (Fig. 1). Among those with concomitant endocrine disease 16.36 % (9/55) have died, whereas in SLE patients without endocrine disease the figure was 15.16% (99/653). That result is not statistically significant by Chi-square.

The most common cause of death in the group with endocrine disease was sepsis (3). Other causes were: cerebral haemorrhage (1), large granular lymphocyte leukaemia (1), pulmonary hypertension (1), cancer (1), heart failure (1) and unknown (1). 88.8% were Caucasian and only one patient was Asian. Seven patients were on high doses of corticosteroids (>20 mg of prednisolone) plus immunosuppressive treatment; one patient only was on medium doses of corticosteroids (from 10 to 20 mg of prednisolone) and the other was on low doses of corticosteroids (<10 mg of prednisolone).

Among the SLE patients without endocrine disease, the most common causes of death were infection (28%) and cancer (26%). Other causes were: heart failure, pulmonary embolism, haemolytic anaemia, myocardial infarction, suicide and liver failure. In this group, 63.6% were Caucasian (63/99); 24.2% were Afro-Caribbean (24/99), 11.1% were Asian (11/99) and only one was South-Asian.

Discussion

Our study focused on a careful review of the 708 SLE patients cohort at UCLH followed for almost 40 years to determine how often endocrinopathies occurred. We found that the most frequent diseases were hypothyroidism (37/708, 5.22%), hyperthyroidism (10/708; 1.41%) and T2DM (10/708; 1.41%). Other endocrine disorders observed were primary hyperparathyroidism (1/708, 0.14%), secondary hyperparathyroidism (4/708; 0.56%) and T1DM (3/708, 0.42%). Isolated cases of hypoparathyroidism and panhypopituitarism were identified.

A close relationship between the immune and endocrine system is well established (20-23). Although concomitant endocrine diseases are not the most common or feared complications for SLE patients, they are important to diagnose and treat. The symptoms caused by endocrinopathies may closely mimic the clinical problems due to SLE, but the treatment is often very different. Thus, thyroxine may well resolve a lupus patient's fatigue if it is caused by hypothyroidism rather than lupus activity.

The prevalence of hypothyroidism in Great Britain is around 1–2% and is 10 times more common in women than in men (some studies in Northern Europe, Japan and USA found the prevalence range between 0.6 and 12 per 1000 women and between 1.3 and 4.0 in men investigated) (25). Our cohort had a percentage of clinical hypothyroidism of 5.22%. While the literature confirmed an increased rate of hypothyroidism in SLE patients, the prevalence rates in different studies differ substantially. Ong *et al*. (2), Antonelli *et al*. (6) and an earlier study from our UCLH cohort (4), showed similar results to this report (3.7%, 5.9% and 5.7%, respectively), whereas other studies such as Molina *et al*. (11) and Domingues *et al*. (13) reported a higher prevalence (19% and 21.5%, respectively). This difference is probably explained by the inclusion in these latter studies of both the clinical and subclinical hypothyroidism.

The prevalence of hyperthyroidism in Great Britain is around 0.2–2% in women and 10 times less prevalent in men in iodine-replete communities (25). 1.41% of patients in our cohort (10/708) had this endocrine disease, a figure within the range of the general population. The literature shows slightly higher results in terms of the frequency with which hyperthyroidism complicates SLE. Thus, Watad *et al*. (1) and Ong *et al*. (2) reported 2.59% and 2.6%, respectively. Chan *et al*. (14) reported a prevalence of 5.8% of hyperthyroidism in a study of 69 SLE patients. However, only 2.9% had a clinical hyperthyroidism, a figure thus closely resembling our results.

It is possible we have under-estimated the prevalence of autoimmune thyroid disease. In a previous study we reported the prevalence of anti-thyroglobulin and anti-microsomal thyroid antibodies is 13.5% and 12.5% respectively in the first 500 patients in the cohort (32). However, we had a low threshold to repeat the thyroid function test throughout the follow-up on our patients so we believe that the number of patients with clinically overt hypo (or hyperthyroidism) thyroid disease is likely to be accurate.

The prevalence of diabetes mellitus in the general population in Great Britain is about 9% (according to Diabetes UK) and 10.4% (27) in Spain (both studies reported around 10% of T1DM and 90% of T2DM). Only 1.83% of patients in our lupus cohort had this concomitant disease. Similar results to ours (1.85%) in a previous study of our UCLH cohort (7) and a slightly higher prevalence was reported by Gallego *et al*. (10) (3.3%) in a cohort of 304 SLE patients reviewed in Spain. Thus, the prevalence of diabetes mellitus seems to be much lower in the different SLE cohorts compared to the general population. The reason could be that lupus patients are mostly diagnosed at an

early age (between 15–45 years old) while, it is well established, that T2DM is more likely to develop over the age of 45 years and this increase becomes exponential from 60 years (24, 28).

Reviewing the literature, we did not find any report linking SLE and hyperparathyroidism. In our cohort, 0.70% of patients reviewed (5/708) had both. In four patients, it was probably a secondary hyperparathyroidism due to lupus kidney disease. One SLE patient had primary hyperparathyroidism as a result of a parathyroid adenoma. Thus, the presence of hyperparathyroidism in patients with lupus is most likely to be linked to renal disease as a result of lupus.

None of our SLE patients have developed Addison's disease.

In our series (in general), the endocrine disease tended to develop after the SLE diagnosis. Thus, we observed this sequence in patients with T2DM (9/10, 90%) or hyperparathyroidism (5/5; 100%). Around 60% of patients with hypothyroidism (17/28) and hyperthyroidism (6/10), developed their endocrine disease following the Lupus diagnosis. However, T1DM was an exception. Each of the three T1DM patients developed the problem before the lupus diagnosis.

A greater risk of having a second endocrine disease was identified in those patients with SLE associated with an endocrine disorder. In those with hypothyroidism, we observed that 32.43% (12/37) had more than one endocrine disease, the most common being T2DM. Among those SLE patients with hyperthyroidism, 10% developed a second endocrine disease. The occurrence of second endocrinopathy in the other endocrine diseases varied; T1DM and T2DM (46.15%) and hyperparathyroidism (60%). Hypothyroidism was the most common second endocrine disease in these different patients.

All the patients with diabetes mellitus (type I and II) who had developed a second endocrine disease (6) had hypothyroidism. 50% (6/12) SLE patients with hypothyroidism who had a second endocrine disease developed T2DM. Subekti *et al*. (26) observed a higher occurrence of hypothyroidism in patients with T2DM.

We analysed our cohort to determine whether those SLE patients who developed endocrine disease concomitantly had a poorer prognosis. The occurrence of death in SLE patients was similar in both groups (16.36% with endocrinopathy *vs*. 15.16% without endocrine disease).

Conclusion

In our cohort of 708 SLE patients followed for almost 40 years, we report a concomitant endocrinopathy in 7.76%, the most common being hypothyroidism (5.22%). Interestingly, 21.8% of our SLE plus endocrinopathy patients also have an increased risk of developing a second endocrine disease. However, our SLE patients with a concomitant endocrine disease had similar outcomes (in terms of death) compared to those without an associated endocrine disease.

Our data are broadly in line with results from other studies, but the number of patients we have studied was generally bigger and our follow-up was much longer. It is important to capture endocrine diseases in SLE as the symptoms they cause may mimic SLE features but require quite distinct treatment.

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