


REVIEW

Thyroid Disease in Lupus: An Updated Review

Yael Klionsky  and Maria Antonelli

In the following review, we seek to provide an overview of the current understanding of various thyroid manifestations affecting patients with systemic lupus erythematosus (SLE), including topics ranging from thyroid-related complications to SLE in pregnancy. Autoimmune diseases tend to coincide, and an association between thyroid disease and SLE has been reported for more than 50 years. There is no evidence that the coexistence of thyroid disease and lupus alters the disease course or manifestations of either. Both hypothyroidism and thyroid nodules are seen more frequently in patients with SLE than in the general population. The rate of thyroid cancer is twice as prevalent in patients with SLE compared with those without SLE. Several forms of thyroid disease are more common among patients with SLE, with adverse consequences in pregnancy. Future work will require delineating the mechanism behind these associations and understanding the role of antirheumatic agents with concomitant thyroid disease.

INTRODUCTION

Systemic lupus erythematosus (SLE) is known for diffuse end-organ effects. Thyroid disease has been associated with the presence of SLE in numerous studies (1–3). Symptoms of thyroid disease and lupus can be confused given that they both have non-specific features, including fatigue, weight change, dry hair, and skin manifestations. In 1961, the first associations between thyroid abnormalities and lupus were described (4). The first prospective study of thyroid disorders in patients with SLE was performed in 1987, and it was concluded that abnormal thyroid function test results are frequently found in patients with SLE (5). Since then, studies have repeatedly observed that thyroid dysfunction is more frequent in patients with lupus compared with the general population (6). Here we provide an updated summary of thyroid disturbances that have been observed in patients with SLE.

METHODS

A search was performed in PubMed, The Cochrane Library, and Ovid-Medline. Phrases used in the search were suited for each individual database and included “SLE AND hypothyroidism,” “SLE AND hyperthyroidism,” “SLE AND sick euthyroid,” “SLE AND thyroid nodule,” “SLE AND thyroid cancer,” “SLE AND Pregnancy AND thyroid,” and “SLE AND fertility AND thyroid.” Our search period spanned from 1946 to 2018. A total of 234 articles were

found. These articles were then assessed for relevance and quality by the authors. Only studies published in English were included. Forty-five of these articles were included as part of this review. A manual review of the references in each of the cited sources was performed to ensure that any relevant resource was not excluded.

Articles were selected as relevant if they 1) were prospective or retrospective studies or meta-analyses involving women with confirmed SLE and 2) reported prevalence or incidence of thyroid dysfunction based on the level of antithyroid antibodies, serum triiodothyronine (T3), serum thyroxine (T4), or thyroid-stimulating hormone (TSH). Articles were excluded if they 1) were case reports, systematic reviews, abstracts, or expert opinion articles; 2) did not include an analysis of SLE disease activity; 3) did not include an assessment of thyroid function, as outlined above; or 4) included patients who had any active pituitary dysfunction.

PATHOPHYSIOLOGY

It is unclear how the pro-inflammatory immune state caused by SLE impacts thyroid function (7). A strong commonality seen between thyroid disease and SLE appears to be the immune predominance of T helper 1 (Th1) cells. Autoimmune thyroid diseases (AITDs), such as Hashimoto thyroiditis and Graves disease, are relatively rare diseases, with 69 cases per 100 000 being diagnosed per year in the United States. There is a greater preponderance of these diseases in women versus men (8). Among

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patients with Hashimoto thyroiditis, antibodies against thyroid peroxidase (TPO) were found in 17% of women and 8.7% of men (9). Both SLE and AITD share elevations in interferon gamma and its associated chemokines. Interferon gamma is one of the main cytokines produced by Th1 cells (10). Despite the theoretical and plausible immunological association seen between SLE and thyroid disease, the clinical correlations vary according to the context of the thyroid disease.

HYPOTHYROIDISM

The most common thyroid disease in patients with lupus is hypothyroidism. Primary hypothyroidism occurs in 15% to 19% of patients with lupus (1,11,12). This frequency is significantly higher than that of the general population, which is approximately 4.6%, as reported in the National Health and Nutrition Examination Survey (NHANES) database (8). In comparison with healthy controls, there is a greater frequency of hypothyroidism in patients with lupus in every age group. This increased prevalence is highest among patients under 20 years of age (odds ratio [OR] 8.38; 95% confidence interval [CI] 2.71-26.01) (11). Female patients with SLE also tend to have a greater likelihood of having both clinical and subclinical hypothyroidism compared with male patients (12). Nevertheless, even among male patients with lupus, compared with healthy male controls, there is a stronger association of hypothyroidism (OR 5.26; 95% CI 3.61-7.68) (11).

Increasing clinical evidence shows a correspondence between severity of outcomes in both diseases. Dong et al (13) observed 363 patients with SLE and subclinical hypothyroidism (elevated TSH levels in the setting of a normal serum free T4 level) for six months and showed that a delay in treatment of subclinical hypothyroidism delays remission of SLE. In addition, the course of SLE can affect thyroid disease. Gao et al (14) performed a case-control study of 1006 patients with SLE and showed that patients with lupus nephritis had persistent subclinical hypothyroidism.

The association among these diseases was further evaluated by a prospective cohort study by Domingues et al (15) of the extent of thyroid disease in 79 patients with SLE and 159 control patients with AITD. Patients with thyroid dysfunction and concurrent SLE activity demonstrated that their duration of SLE disease activity was prolonged, compared with those without thyroid dysfunction ($P < 0.05$). Patients with SLE with anti-Smith antibodies were also more likely to exhibit hypothyroidism ($P < 0.05$), potentially suggesting an immune link between the two diseases (15). Given this study's heterogeneous control group and lack of any confounder analysis, the associations found require confirmation in a larger data set.

An Israeli study of 77 patient with SLE and 52 healthy controls saw no difference in antithyroglobulin or anti-TPO antibody levels between the groups, despite an 8.7% greater prevalence of hypothyroidism in their SLE population ($P = 0.048$) (2). Overall,

these studies highlight the link between the presence of lupus and various levels of hypothyroidism.

HYPERTHYROIDISM

Hyperthyroidism seems to occur in patients with SLE at a marginally higher rate compared with the general population but less frequently than hypothyroidism. In the general population, the prevalence of hyperthyroidism has been reported as 1.3% (2,8). In patients with SLE, hyperthyroidism rates vary from in 3% (6) to upward of 9% of the population (12).

Treatment of hyperthyroidism in the setting of SLE does not differ from that in patients without SLE. Options range from antithyroid medications to radioactive ablation and thyroidectomy. Patients who have SLE and take antithyroid medications can have a more complicated response if they suffer adverse effects from the medication. Patients without SLE can develop symptoms while on medication that mimic SLE. Specifically, the antithyroid medications methimazole and propylthiouracil can cause adverse effects that mimic SLE symptoms. These symptoms include low white blood cell counts, thrombocytopenia, arthralgias, nephritis, alopecia, and leukocytoclastic vasculitis and have even been associated with a lupus-like syndrome (16,17). Aside from a few case reports, no consistent link has been made between use of antithyroid medications and the prolongation or onset of SLE. Furthermore, a recent meta-analysis showed no statistical link between hyperthyroidism and SLE (18).

SICK EUTHYROID SYNDROME

Nonthyroidal illness syndrome (NTIS), also known as sick euthyroid syndrome, is associated with acute and chronic systemic conditions seen in a variety of settings. Defined by laboratory values, these patients have decreased concentrations of total T3 and free triiodothyronine (fT3), low T4 levels, and a normal-range or slightly decreased concentration of TSH (19). NTIS has been described in patients in various medical setting, including patients with SLE, patients requiring treatment in an intensive care unit, patients with severe infections, and patients after the ingestion of medications, including amiodarone, corticosteroids, and propranolol (20).

Steroids, especially at high doses, and immunosuppressants can affect thyroid function by suppressing TSH (21). Although they often do not cause clinically evident central, that is, pituitary or hypothalamus-based, hypothyroidism, these medications can contribute to sick euthyroid syndrome (20,21). Fluctuation of thyroid function with lupus disease activity as measured by SLE disease activity index (SLEDAI) scoring has been reported, making estimation of the prevalence of the sick euthyroid state in a lupus population somewhat difficult. It has been suggested that approximately 8% to 9.5% of patients with lupus are in a sick euthyroid state (22–

24). Given the known depressive effect of glucocorticoids on thyroid function, this suggests the possibility that high doses of glucocorticoids taken by patients with SLE during acute disease flairs could contribute to depressing thyroid dysfunction (25). Unfortunately, no studies evaluating the effects of steroids on thyroid function in adult SLE populations have been published.

AUTOIMMUNE THYROID DISEASE

The coexistence of thyroid disease in patients with SLE should not be a surprise given the autoimmune pathogenesis that is characteristic of both diseases. There is emerging evidence to suggest a genetic basis for the association between SLE and thyroid disease. Patients carrying a particular R620W polymorphism in the *PTPN22* gene encoding a T-cell protein are more likely to develop concurrent SLE and thyroid disease and not SLE alone (25). In addition, in a study of families with both SLE and thyroid disease, a site on chromosome 5 (5q14.3-15) was reported to be a susceptibility gene shared by patients with SLE and AITD (15).

Numerous studies confirm that a relatively high number of patients with SLE have antithyroid antibodies, with values ranging from 20% to 45% in patients with SLE, compared with 10% in the general population (6). Another study evaluated patients with SLE over a 6-month period and found the prevalence of antithyroid antibodies to be similar between patients with SLE (21%) and healthy controls (16%) (26). Based on a recent meta-analysis covering a total of 1076 patients with SLE and 1661 controls, the prevalence of thyroid autoantibody positivity in patients with SLE compared with healthy controls is consistently high, with an OR of 2.99 (95% CI 1.83-4.89) (27).

Interestingly, it seems that antithyroid serologies may fluctuate over time within the same SLE patient population. It was reported that clinical thyroid disease in SLE was associated with the persistence of antithyroid antibodies (28). Conversely, patients with established AITD are at a significantly higher risk for developing lupus. For example, women with Graves disease or Hashimoto thyroiditis are at greater than 10-fold risk of developing lupus (risk ratio [RR] 11.69 [95% CI 6.23-20.0; $P < 0.001$] and RR 14.64 [95% CI 3.02-47.5; $P < 0.001$], respectively). Men with Graves disease have a greater than 80-fold risk of developing lupus (RR 84.39; 95% CI 10.22-303.16; $P < 0.001$) (29).

THYROID CANCER

Patients with lupus have higher rates of many types of cancers compared with the general population (30). Most common among these are hematologic and certain solid organ malignancies (31). The rate of thyroid cancer in patients with lupus, noted to be 0.1%, albeit low, is approximately twice that seen in the general population (32). Moreover, among patients with lupus with papillary thyroid cancer, AITD was noted in 80%, a much higher

rate than in patients with SLE without cancer (30%) (33). These results are consistent with a recent retrospective analysis of the prevalence of AITD in patients following thyroidectomy (34). In that study, SLE treatment did not appear to be related to the presence of thyroid cancer (35).

A recent meta-analysis comprising 16 studies and 59662 patients with SLE reviewed overall malignancy rate and showed a pooled RR of 1.28 (95% CI 1.17-1.41) for overall malignancy and a pooled RR of 1.78 (95% CI 1.35-2.33) for thyroid cancer (34). In one Japanese study of 53 patients with rheumatic conditions, including SLE, the authors found an increased likelihood of thyroid cancer development if lymphadenopathy/splenomegaly or weight loss was present during treatment of SLE (36). Given the number of robust studies, having SLE likely increases the risk of having thyroid cancer, emphasizing greater vigilance for any thyroid nodules or aberrations in thyroid activity.

THYROID NODULES

The presence of thyroid nodules in SLE has not been evaluated throughout the literature as thoroughly as other aspects of thyroid disease. However, thyroid nodules also appear more commonly in patients with SLE. Compared with iodine-sufficient controls, the prevalence of thyroid nodules is higher in patients with lupus (25% versus 13%; $P = 0.001$) (37). This is consistent with the reported prevalence of thyroid nodules in Hispanic patients with SLE in a prospective case series (38). In addition, demographics may also play a role. A Chinese study demonstrated that 1% of the Chinese SLE population was noted to have thyroid nodules (37). SLE medication has been associated with the development of thyroid nodules. Specifically, the prevalence of thyroid nodules was correlated with previous azathioprine use. Of importance, none of the nodules in the study were malignant (39).

THYROID DISEASE IN PREGNANCY

Because of the normal hormonal changes of pregnancy, women experience almost a twofold increase in their thyroid-binding globulin concentrations (3). This leads to an increase in the total T3 and T4 levels but not in the free concentrations of both hormones (40). Despite these changes, Moleti et al (41) demonstrated that during pregnancy, patients with SLE have both increased fT3 and T4 levels and an increase in thyroid disease compared with their counterparts without SLE. Yet, there is no difference in SLE activity during pregnancy between those patients with thyroid disease and those without thyroid disease (42). This suggests SLE may be an independent driving factor behind clinical thyroid disease in pregnancy. Although no concrete mechanism has been determined, several clues exist in the literature. First, there is likely an immunological link driving SLE and AITD. Several case reports and case series have reported a 19% to 43% prevalence of anticardiolipin antibodies in patients with

AITD. Antiphospholipid syndrome, of which anticardiolipin is one of the characteristic antibodies, has been recognized as one of the most treatable causes for recurrent miscarriage. In one retrospective cohort study comparing antithyroid antibody-positive and antithyroid antibody-negative patients, those with the antithyroid antibodies had a significantly higher percentage of antiphospholipid antibodies compared with those without (13.8% versus 2.4%) (43,44). Further work on pregnancy outcomes in a cohort of 150 women showed that of those with a major rheumatic disease, such as SLE, 60.7% had antithyroid antibodies, such as anti-TPO or antithyroglobulin, compared with 8% of controls.

There may also be differences in both implantation, miscarriage rates, and perinatal outcomes. In one small retrospective study, there was a trend for an increased miscarriage rate for women with lupus and thyroid disease (15% of 20 patients) compared with women with lupus and no thyroid disease (3% of 36 patients) (41). Furthermore, this study indicates that women with concomitant SLE and thyroid disease have a significantly increased rate of preterm birth compared with patients with lupus without thyroid disease (67% versus 18%; $P = 0.002$) (45). This risk for preterm birth was increased irrespective of adequate thyroid treatment with levothyroxine. There was no difference in mean delivery weights in women with SLE with thyroid disease compared with those without thyroid disease. Finally, the authors described no association between the presence of thyroid antibodies and preterm birth rates.

Although there is no specific thyroid disease that is unique to patients with SLE, an association between the spectrum of thyroid disease and SLE has been reported for more than 50 years. Hypothyroidism is the most common thyroid disease in patients with lupus, and both diseases likely share a common immunological etiology. Both hyperthyroidism and thyroid nodules are more common in patients with SLE than in the general population. Although the thyroid cancer rate in lupus is low, it is twice as prevalent in these patients compared with those without SLE. Women with SLE and thyroid disease have been found to have higher rates of preterm delivery compared with women with SLE and no thyroid disease. In short, despite the varied presentation and effects of thyroid disease, the rheumatologist should seriously consider the implication of any manifestation of thyroid disease in any patient with lupus.

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AUTHOR CONTRIBUTIONS

Drs Klionsky and Antonelli drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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