Review

Environment and systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a wide range of clinical manifestations and a relapsing-remitting course. SLE pathogenesis is the result of complex interactions between ethnic, genetic, epigenetic, immunoregulatory, hormonal and environmental factors, and several aspects of these multifactorial connections are still unclear. Overall, for the disease development, an environmental trigger may induce immunological dysfunction in genetically predisposed individuals. This review aims to summarise the most relevant data on the impact of environmental factors on the incidence of SLE and on disease activity and damage in patients with an established diagnosis of SLE.

Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disease with a broad spectrum of clinical manifestations, that mainly affects young women (1). The aetiology of SLE is multifactorial, encompassing genetic, epigenetic and environmental factors. The role of genetics in SLE is suggested by mouse models, familial linkage studies and concordance of the disease in twins (2-4). However, a recent metastudy on SLE concordance in twins revealed high rates of discordance (up to 75% in monozygotic and to 95% in dizygotic twins) (5), confirming the key role of environmental factors in SLE susceptibility. This narrative review focuses on the main environmental factors involved in the development and course of SLE.

Environmental factors involved in SLE

Ultraviolet (UV) light

Among environmental factors, UV radiation exposure is recognised as a risk factor for the development and reactivation of SLE. Whereas UVC, with its short wavelength, does not penetrate the atmospheric ozone layer, UVA (320–400 nm) and UVB (280–320 nm) are environmentally relevant.

UVA penetrates the deeper dermis and is weakly absorbed by cells: its role in SLE pathogenesis is still unclear. Indeed, some studies have found that UVA induces a reduction in disease activity in SLE patients and in patients with cutaneous lupus erythematosus (CLE) (6); conversely, other studies have shown that UVA exposure induces lupus skin lesions (7, 8). In contrast, UVB is unable to penetrate the epidermal layer and is more absorbed by DNA and cellular proteins; therefore, UVB is the most effective inducer of keratinocytes apoptosis. Several phototesting studies demonstrated as UVB and/or UVA can induce skin lesions in patients with different subtypes of LE (9), proving that UV radiation exposure may induce or exacerbate skin manifestations, while their role as risk factors for the development of SLE remains unclear. Only a few case-control studies have been able to examine UV radiation exposure and risk of SLE (10, 11).

As we know, UV radiation causes DNA damage and apoptosis of keratinocytes; apoptotic keratinocytes, known as "sunburn cells", are characterised by eosinophilic cytoplasm and pyknotic nuclei and can be found as early as eight hours after UV exposure (12). UVA induces keratinocytes apoptosis mainly through mitochondrial oxidative damage leading to increased production of reactive oxygen species (13). Conversely, UVB induces apoptosis through DNA damage with strand breaks and pyrimidine dimers formation (14). Kuhn *et al*. showed that, after a single UV light exposure, apoptotic cells accumulate in the skin of patients with CLE, com-

pared to controls, suggesting impaired or delayed clearance (15).

Another mechanism through which UV induces skin injury is by increasing autoantigens production in the epidermis, such as Ro52, IF116, Sm, RNP, Ku and ribosomal-P (16). Moreover, UV light increases the expression of chemokines and induces keratinocytes and immune cells to release pro-inflammatory cytokines such as interferon (IFN) and tumour necrosis factor alpha (TNFα). Furthermore, even in healthy skin, UV induces the upregulation of proteins that act as autoantigens in SLE patients, suggesting that chronic or intense UV exposure can increase the tendency to autoantigen exposure (16).

Silica

Of the chemical agents that act as triggers for SLE development, silica has been the most studied. Silica is commonly found in nature as quartz; exposure to respirable crystalline silica (<10 μm) occurs most often in occupational settings.

Several epidemiological studies have shown that silica exposure is related to the development of autoimmune diseases such as rheumatoid arthritis, ANCA-associated vasculitis, systemic sclerosis and SLE (17). Both Parks *et al*. (18) and Morotti *et al*. (19) reported that occupational silica exposure may be associated with SLE, particularly in patients with silicosis. The dose-response has been associated with increasing intensity or duration of exposure (18, 20); these findings are confirmed by other population-based studies (21, 22). Interestingly, patients with SLE and silicosis are predominantly middle-aged and elderly men, in which the age of SLE onset has been found to be between 40 and 63 years (23).

Smoking

Cigarette smoking has also been associated with the development and progression of several autoimmune diseases, including SLE (24).

The pathogenetic link between smoking and SLE development remains debated; potential mechanisms include oxidative stress, increased cytokine-driven systemic inflammation and impaired T- and B-cell function, epigenetic modifications. In particular, cigarette smoke increases CD95 expression on B and T lymphocyte cell surfaces (25); CD95 plays a central role in immune homeostasis, being an essential membrane receptor for transmitting apoptosis signals in lymphocytes; as a consequence, its increased expression could be responsible for increased apoptosis leading to an overburdening of apoptotic debris clearance mechanisms, a major driver of autoimmunity in SLE. Other potential cellular mechanisms include reduction and functional impairment of natural killer cells and impairment of Th17 and Th22 cells functions.

The causal association between smoking and disease onset risk, antibodies profile, organ damage and treatment efficacy in SLE patients has been the focus of extensive investigations in recent years.

The relationship between smoking exposure and the risk of developing the disease is still debated; the presence of possible confounders and the low incidence of the disease in the general population would require big cohorts to be followed and analysed to draw sound conclusions; to overcome these difficulties, several metanalysis have been published in the last years.

In 2019, a metanalysis of 9 case-control studies by Parisis *et al*. (26) found a significantly increased risk of SLE in current-smokers compared to never-smokers and in ever- *versus* never-smokers, while former-smokers were not at increased risk of SLE. Data on passive smoking remain scarce and controversial. In the same study, no over-risk of anti-dsDNA, anti-Sm or anti-SSA positivity was observed according to smoking status.

More recently, Chua *et al*. (27) published a metanalysis using a Bayesian approach, including 12 studies for a total of 3234 individuals who developed SLE and 288336 control subjects; the study confirmed the association between current smoking and the risk to develop SLE; interestingly, in this meta-regression analysis, publication time, age and gender did not have a significant effect on the disease occurrence risk.

Moreover, in 2006, Simard *et al*. (28) investigated whether early-life exposure to cigarette smoke was associated with subsequent SLE development; to this end, they examined approximately 18000 adults free of SLE at baseline who provided information on perinatal exposures; in total, 236 incident SLE cases were identified, but maternal cigarette smoking did not increase the risk of SLE nor did paternal smoking during participants' childhood.

The association between tobacco smoking and morbidity and organ damage has been poorly studied.

In the 1990s, Ward and Studenski's study showed a significant association between smoking and the development of end-stage renal disease (29).

More recently, Montes *et al*. (30) investigated the chronic damage accrual expressed by the SLICC/DI in a cohort of SLE patients exposed or not to tobacco smoke. They found that being "never exposed" to smoking confers a 22% relative risk reduction of progressing to an SDI score >0 compared to an "ever exposed" status.

In 2022, a systematic review was published to summarise the available evidence on the effects of tobacco smoking on developing a cardiovascular disease (CVD) in SLE patients (31). The authors included a total of 10 studies on 6984 participants. Compared to never-smokers, the risk of developing CVD in current-smokers was significantly higher.

In the last years, growing evidence has suggested that tobacco smoking could also have an impact in the effectiveness of therapies in SLE patients.

The most recent data on this topic were reviewed by Parisis *et al*. (26); in 11 observational studies of CLE or SLE patients, tobacco smoking significantly reduced the therapeutic effectiveness of hydroxychloroquine (HCQ) in cutaneous lesions. However, some studies evaluated the correlation between plasmatic HCQ levels and tobacco smoking, and no significant differences were found between smokers and non-smokers (32-35).

One single study evaluated the effect of tobacco smoking on the clinical response to belimumab (36). In a prospective follow-up study that included active SLE patients starting belimum-

ab, the authors observed that current smokers showed decreased probability and prolonged time to attain clinical response compared to non-smokers. The same group also demonstrated that current or former smokers showed a higher probability of unchanged/worsened mucocutaneous manifestations compared to never-smokers, while no impact of smoking on belimumab efficacy in articular SLE was reported (37).

In conclusion, available evidence suggests that tobacco smoking exposure is associated with SLE disease risk, its clinical progression/damage and response to treatment. However, it is important to note that the available studies refer to a wide range of geographical locations, vary widely in smoking exposure collection methods and SLE phenotype; thus, large prospective studies could be encouraged to better explore the complex interaction between the disease and tobacco smoke. Moreover, there is a large and intriguing area related to the possible impact of heated tobacco products and electronic cigarette smoking, for which no studies exist yet.

Infections

Exogenous microbial agents, such as bacteria or viruses, interact with and sometimes overcome the human immune system, potentially leading to autoimmunity. Among microbiological agents, viruses in particular have been implicated as potential triggers of autoimmune conditions (38, 39). Overall, viral infections could interact with innate and acquired immune responses and lead to an aberrant response or lack of immune control, facilitating the development of SLE and other autoimmune diseases. From an aetiopathogenetic point of view, the mechanism of molecular mimicry by specific microbial agents might play a role in the development of SLE.

Several studies on the association with Epstein-Barr virus (EBV) have been conducted over the years, with conflicting results (40). The main findings on the positive association come from studies focusing on seroconversion rates in SLE patients.

Some papers reported an association between SLE and not only seroconversion but also the presence of EBV genome in peripheral blood lymphocytes in children and teenagers (41, 42). Concerning adults, a study involving 196 SLE patients tested for previous infections demonstrated that all but one had been exposed to EBV, whereas no differences were observed between SLE patients and controls in seroconversion against CMV, HSV-2, or VZV, supporting the possible role of EBV in the development of SLE (43). Similar results emerged from another case-control study, where a significant difference between SLE patients and controls was also found in EBV viral load, with the EBV-DNA positivity rate tending to decline with age in the latter but not in the former (44).

In 2014, Hanlon *et al*. published a metanalysis of 25 case-control studies to determine whether prior EBV infection occurs more frequently in SLE patients compared to matched controls: although publication bias cannot be excluded, the metanalysis supports the hypothesis that EBV infection predisposes to SLE development (45). Indeed, significantly higher seroprevalence of anti-viral capsid antigen (VCA) IgG, anti-early antigen (EA)-D IgG and anti-VCA IgA emerged in cases compared with controls.

A seroprevalence of almost 100% suggests a significant, although not entirely clear, role of EBV infection in SLE pathogenesis. The likelihood that EBV infection causes SLE in some patients is supported by the possible molecular mimicry of the EBV peptide PPPGRRP by the human spliceosome peptide SmB'/B's PPPGMRPP (46). Moreover, the presence of a dominant epitope in the C-terminal region of SmD, which exhibits a striking resemblance to a region of the EBV nuclear antigen coding for the EBNA1 protein (47), has previously been demonstrated, thus raising hypotheses on the possible role of the immune response to EBV in the induction of anti-SmD antibodies (48). Besides, the cross-reactivity of spontaneously developed anti-ribosomal P protein antibodies with the B/B´ and D constituents of the Sm complex has been proven (49).

Recently, potential underlying molecular mechanisms have been investigated by genetic and transcriptomic analyses: lower latent EBV markers and higher lytic EBV markers were found in lymphoblastoid cell lines (LCLs) of SLE patients compared to healthy individuals, suggesting an EBV nuclear antigen 2 (EBNA2)-mediated molecular pathway in which SLE risk loci may increase the tendency of LCLs to switch to the lytic phase (50).

A case-control study published a few months ago, with data on serological, molecular and sequence markers of EBV infection in SLE patients, demonstrated a 24-fold higher chance of having SLE in the presence of anti-EBV-EA-D IgG antibodies (51). Furthermore, higher titres of anti-EBV-EA-D IgG were identified as independent factor associated with lymphopenia and SLE haematological manifestations, while a higher titre of anti-VCA IgG as an independent factor associated with alopecia in SLE.

Regarding other infections, the Carolina Lupus Study showed that the risk of SLE increased with a history of shingles and with frequent colds in the three years prior to diagnosis (52). A recent systematic review suggested a potential association between COVID-19 and new onset of systemic autoimmune diseases, mostly myositis and SLE (53), although given the few cases and the short follow-up period no firm conclusions can be drawn to date.

It should be noted that infections might not only be associated with the development of SLE, but also act as triggers for disease flares over time. Among the viral infections of most interest, influenza was found to be a risk factor for a SLE flare according to a recent study, with an incidence ratio for flares of 25.75 during the risk interval compared to the control interval (54).

Even more, the possibility that the infection itself acts as a mimicker for a SLE flare (55) should not be underestimated. SLE patients, in fact, are a population at increased infection risk due to both the aberrant immune system and glucocorticoids and other immunosuppressants used to treat the disease. Although prognosis has considerably improved over the years, infections still remain a major cause of hospitalisation

and mortality in patients with SLE, especially in the early phase of disease (56-58).

Although controversial, the crucial interplay between SLE and infections must draw attention to the importance of preventive measures such as vaccination.

Exogenous hormones

Sex hormones may play a role in pathogenesis, clinical features and management of SLE.

A correlation between incident SLE and use of combined oral contraceptives was described by Bernier *et al*. (59) in a large ten-year cohort. Data from this study suggested a possible acute effect of sexual hormones in susceptible women, as an increased risk of SLE was observed particularly in women who had recently started hormone therapy and increased with the dose of ethinylestradiol.

A unique population is represented by transgender women receiving female sex hormones before or after sexual reassignment surgery. Few cases of transgender women who have been diagnosed with lupus following use of exogenous female sex hormones were reported (60-64). None of them had a previous lupus diagnosis, and renal involvement was described in three cases (60, 63, 64). Despite the low number, these data focused on the potential relationship between female sex hormones and SLE in susceptible individuals.

It is known that SLE predominantly affects women, and patients may require hormone therapy during their life. Several clinical trials have investigated the effects of hormone therapies in SLE patients, with a particular attention to oral contraceptives and menopause hormonal therapy.

In a randomised controlled trial (RCT) on 162 SLE women, patients were randomised to combined oral contraceptive, progestin-only pill or copper intrauterine device (65). The results demonstrated the absence of influence of these contraceptive methods on disease activity and adverse events in this SLE subgroup. In another RTC on 183 SLE women, the authors observed that combined hormonal oral contraceptives did not increase the risk of disease flare compared to placebo (66).

In both studies, all patients had stable disease and those with medium/high titre of antiphospholipid antibodies (aPL) were excluded, as well as patients with history of thrombosis. Of note, in the first study (65) thrombosis occurred in four patients (two for each group receiving hormones), and all four patients had low aPL titres.

Conversely, studies on effects of combined contraceptives on aPL-positive patients showed an increased risk of thrombosis. A large multicentre population-based case-control study, named RATIO (Risk of Arterial Thrombosis In relation to Oral contraceptives) (67), showed an increased risk of arterial events in combined users compared with non-users. In particular, lupus anticoagulant (LAC) resulted a major risk factor for arterial thrombotic events, and the risk of myocardial infarction and ischemic stroke increased further in women who used combined oral contraceptives.

As a matter of the fact, scientific societies (EULAR and ACR) support the use of combined hormonal contraceptives in patients with stable/inactive SLE and negative aPL, while in women with positive aPL contraception with combined hormones should be discouraged and progesterone only contraception carefully weighed against the risk of thrombosis (68, 69). Moreover, ACR conditionally recommends against the use of transdermal oestrogen-progestin patch, since it results in greater estrogen exposure than oral or transvaginal methods (70).

In SLE patients with menopausal symptoms, hormone replacement therapy (HRT) seems to improve vasomotor symptoms (71), and several studies have investigated HRT impact in SLE women.

In RCTs no significant increase in severe disease flares (72, 73) or cardiovascular (CV) events (74) was reported in SLE patients receiving HRT compared to controls. However, Buyon *et al*. observed a small increase in mild-moderate flares in SLE HRT group with respect to placebo (1.14 *vs*. 0.86 flares/person-year for HRT and placebo, respectively) (73). We must acknowledge that women with high disease activity, previous thrombosis or aPL-positivity were excluded from most studies.

As stated in the previously mentioned EULAR and ACR recommendations (68, 69), HRT should be reserved for the management of severe and disabling menopausal vasomotor symptoms, preferably in SLE women with stable/inactive disease and negative aPL, while in patients with positive aPL the use of HRT should be discouraged or carefully weighed against thrombotic and CV risks.

Diet

Some macronutrients and micronutrients seem to have antioxidant, anti-inflammatory and immunomodulatory effects, and over the years several studies have investigated their impact on rheumatic and musculoskeletal diseases (RMDs) and SLE (75). However, we must consider that most of the studies are pilot or small samples studies, and thus reliable conclusions cannot be drawn.

Overall, a healthy, balanced diet is integral to lifestyle improvement for people with RMDs (76). However, patients should be informed that consuming specific food types is unlikely to have large benefits for RMD outcomes.

CV risk is known to be higher in SLE patients, and mediterranean diet has been reported to down-regulate inflammatory biomarkers related to atherogenesis in subjects at high CV risk (77). A cross-sectional study on 280 SLE patients showed that greater adherence to the mediterranean diet correlated with beneficial effect on disease activity and CV risk (78).

In overweight women with corticosteroid-dependent SLE, Davies *et al*. (79) analysed the influence of low glycaemic index diet and calorie restricted diet in a 6-week controlled trial. Both diets led to significant weight loss, improved waist and hip measurements and reduced fatigue. In addition, no disease flares were observed during the study period, confirming the safety of this dietary regimen.

Omega-3 fatty acids are involved in serotonin synthesis (80), and effects of omega-3 supplementation in SLE have

Table I. Principal interventional studies on omega3 supplementation in SLE.

Reference	n	Types of intervention	Duration	Conclusions
Westberg *et al*. 1990 (81)	17	Omega-3 *vs*. olive oil refined (placebo group)	6 months	Short-term beneficial effect on disease activity
Duffy *et al*. 2004 (82)	52	Omega 3 with/without copper *vs*. copper *vs*. placebo	24 weeks	Improvement in disease activity (SLAM-R)
Wright *et al*. 2008 (83)	60	Omega-3 *vs*. olive oil (placebo group)	24 weeks	Improvement in disease activity (SLAM-R, BILAG) and endothelial function; reduction in oxidative stress
Bello *et al*. 2013 (84)	85	Omega-3 *vs*. starch (placebo group)	12 weeks	No improvement in disease activity, endothelial function, nor decrease in inflammatory markers
Arriens *et al*. 2015 (85)	50	Omega-3 *vs*. olive oil refined (placebo group)	6 months	Improvement in PGA, SF-36 and some circulating inflammatory markers; no impact on disease activity
Curado Borges *et al*. 2016 (86)	49	Omega-3; no placebo group	12 weeks	No impact on IL-6, IL-10, leptin and adiponectin; significant decrease of CRP levels and impact on cholesterol levels

been investigated in few studies, with controversial results. Some papers reported benefits from omega-3 supplementation in SLE patients, while other studies did not confirm these results, as shown in Table I.

Vitamin D is often considered an anti-inflammatory agent, and has effects on proliferation, apoptosis and function of immune system cells that are involved in SLE pathophysiology (87). Vitamin D deficiency is common in SLE, since the use of medications such as glucocorticoids and renal failure can alter its metabolism (87). In addition, all SLE patients are advised to avoid sunlight, and vitamin D deficiency is also reported as a potential risk factor for SLE (88).

In clinical setting, adding vitamin D to the traditional pharmacological regimen in SLE has been found beneficial in some studies, whereas other studies failed to replicate these results, as detailed in Table II.

Lastly, only a few studies have evaluated the association between different types of diet and the risk of SLE. According to a recent prospective study, no association was found between dietary patterns and risk of SLE occurrence (98). However, a subsequent study suggested that a diet high in carbohydrates and low in fat may be associated with an increased risk of SLE in African-American women (99).

Gut microbiota

Increasing studies have shown that gut microbiota dysbiosis, inducing inflammation and immune system sensitisation, represents a significant risk factor for the development of autoimmune diseases, such as SLE (100).

In 2014, Hevia *et al*. (101) observed a lower *Firmicutes*/*Bacteroidetes* (F/B) ratio in SLE patients than in healthy people. This finding was confirmed by subsequent studies (102-105); furthermore, a French study observed that F/B ratio was significantly lower in active SLE patients compared to patients in remission (102). A significant decrease in *Lactobacillus* was also found in SLE patients compared with healthy controls (105).

Recently, Xiang *et al*. (106) realised a metanalysis including 11 case-control studies that examined 373 SLE patients and 1288 healthy controls. They observed that SLE patients had fewer *Ruminococcaceae*, but higher levels of *Enterobacteriaceae* and *Enterococcaceae*. A two-sample Mendelian randomisation study (107) found that *Bacilli*, *Eggertella* and *Lactobacillales* were positively correlated with the risk of SLE, whereas *Bacillales*, *Actinobacteria*, *Coprobacter* and *Lachnospira* were negatively correlated with SLE risk.

Another crucial factor involved in SLE pathogenesis is the impairment of intestinal barrier: indeed, leaky gut has been observed in patients with SLE. This finding was demonstrated by two studies that observed how calprotectin levels in SLE stool samples were significantly increased compared to controls (108, 109). Moreover, Azzouz *et al*. (108) observed that serum soluble CD14, α1-acid glycoprotein and lipopolysaccharides levels were higher in SLE patients than in healthy subjects, suggesting the presence of intestinal bacterial displacement.

Molecular mimicry is another potential mechanism linking gut microbiota with SLE, and several microorganisms are involved: *B. thetaiotaomicron*, containing Ro60, induces T- and B-cell responses against human Ro60 and glomerular immune complexes deposition; *E. gallinarum* and *R. intestinalis* induce anti-β2GP1 antibodies secretion; *O. splanchnicus,* presenting a peptide similar to human Sm antigen epitope, increases IFN-γ and IL-17A production; *A. muciniphila* has a peptide that, mimicking human Fas antigen, binds to IgG produced by memory B cells; lastly, *R. gnavus* cross-reacts with anti-dsDNA antibodies.

Gut microbiota dysbiosis leads to both cytokines and immune cells dysregulation, contributing to the development and progression of SLE. Briefly, *E. gallinarum* and *Ruminococcus* are associated with an increase in Th17 cells and a reduction of Treg, with a Th17/Treg imbalance; *E. gallinarum* and *L. reuteri* increase the number of plasmacytoid dendritic cells and promote the production of IFN-I, one of the most important pathogenetic factors in SLE (110).

Drug-induced SLE

Drug-induced lupus (DIL) was first described in 1945 by Hoffman, who reported lupus-like symptoms due to sulfadiazine treatment (111). Since then,

Table II. Principal interventional studies on vitamin D supplementation in SLE.

Reference	n	Types of intervention	Duration	Conclusions
Ruiz-Irastorza *et al*. 2010 (89)	60	Oral vitamin D3; no placebo group	24 months	Beneficial effect on fatigue; no effect on SLE severity
Terrier *et al*. 2012 (90)	20	Vitamin D3 100000 IU/week for 4 weeks, followed by 100000 IU/month for 6 months; no placebo group	6 months	Beneficial effect on immunological and inflammatory markers
Petri *et al*. 2013 (91)	1006	In patients with levels <40 ng/mL vitamin D2 50000 IU/week plus calcium/vitamin D3 200 IU twice daily	128 weeks	A 20 ng/mL increase in vitamin D level was associated with decrease in the odds of having a high disease activity score and of having clinically important proteinuria; no evidence of additional benefit of vitamin D beyond a level of 40 ng/ml
Aranow *et al*. 2015 (92)	54	Vitamin D3 4000 IU/day (high dose group) or 2000 IU/day (low dose group)	12 weeks	No effect on IFN signature in vitamin D-deficient SLE patients
Andreoli *et al*. 2015 (93)	34	Vitamin D3 25000 IU/month (standard regimen) or 300000 IU initial bolus followed by 50000 IU/month (intensive regimen) for one year and then switched to the other regimen in the second year	24 months	Neither regimen of supplementation affects disease activity or SLE serology
Piantoni *et al*. 2015 (94)	34	Vitamin D3 25000 IU/month (standard regimen) or 300000 IU initial bolus followed by 50000 IU/month (intensive regimen) for one year and then switched to the other regimen in the second year	24 months	Enhancement of T-reg cells
Marinho *et al*. 2016 (95)	24	Vitamin D3 at variable dosage during the study period	6 months	Reduction in SLEDAI and improvement in the Treg/Th17 ratio
Karimzadeh *et al*. 2017 (96)	90	Vitamin D3 50000 IU/week for 12 weeks and then 50000 IU/month for 3 months *vs*. placebo	6 months	No effects on disease activity
Al-Kushi *et al*. 2018 (97)	81	Corticosteroid treatment with vitamin D3 1400 IU/day and calcium carbonate 1250 mg/day *vs*. corticosteroid treatment without supplementation *vs*. no corticosteroid treatment	6 months	Vitamin D and calcium supplementation significantly improved the bone mineral density in vitamin D-deficient patients; no effect on immune markers or disease activity

the list of drugs potentially involved in the genesis of DIL has been expanding. DIL is not a typical allergic drug reaction, but is the result of a drug-induced self-tolerance breakdown process (112). According to studies of the early 2000s, 15000–30000 cases of DIL are estimated to occur annually in the United States, meaning that up to 10% of SLE cases may be drug-induced.

Overall, compared to idiopathic SLE, DIL tends to develop in elderly people (partly because more exposed to drugs), has a lower female predominance (with a female-to-male ratio ranging from 4.3:1 to 1:1) and presents with a "lupus-like syndrome" usually characterised by fewer and milder clinical symptoms. Arnaud *et al*. recently updated the list of drugs associated with DIL. In 12166 DIL cases from the WHO pharmacovigilance database, 118 putative drugs were identified, and among these 42 had not been previously reported in association with DIL. DIL was considered definite for nine drugs: procainamide, hydralazine, minocycline, quinidine, isoniazid, terbinafine, methyldopa, dihydralazine and chlorpromazine (113). Although less used nowadays, procainamide and hydralazine are associated with the highest risk of DIL, with an estimated 20% incidence and 5–8% risk per year of treatment (114).

In a recent matched case-control study conducted on incident cases of CLE and SLE in the Danish National Patient Register, new plausible associations were observed with some common drugs: fexofenadine hydrochloride, metoclopramide hydrochloride, metronidazole hydrochloride and levothyroxine sodium (115).

Moreover, a French pharmacoepidemiological study suggested a link between statin exposure and DIL, with a reported OR >1 for each statin but fluvastatin (116).

Several anticonvulsants have been reported to be associated to DIL, including carbamazepine (117) and valproic acid-induced lupus (118).

From a rheumatological perspective, it is worth noting that, according to the WHO pharmacovigilance database, since 2007 onwards, anti-TNF agents have been the drugs most commonly associated with systemic DIL (113). We can speculate if anti-TNF treatment may unmask an underlying SLE in patients with a baseline higher risk of overlap syndrome, rather than cause *de novo* drug-induced lupus (112).

Anti-TNF are known to induce autoantibody production. Specifically, in prospective placebo-controlled trials, anti-

dsDNA antibodies were induced in 20% of infliximab, 15% of etanercept, 10-12% of adalimumab and 4% of certolizumab pegol patients. On the contrary, in TNF-α antagonist-induced lupus-like syndrome (TAILS), anti-histone antibodies are less common (positive in only 17–57% of patients). Moreover, in a review of 72 patients with TAILS, the presence of 12% anti-Ro/La, 10% anti-Sm and 7% anti-RNP antibodies was reported (119).

However, despite a quite high proportion of patients developing autoantibodies during anti-TNF treatment, the development of a clinically relevant lupus-like syndrome is much more infrequent and has been estimated to occur at a rate between 0.5 and 1%. According to a French study, infliximab and adalimumab carry a higher risk of TAILS than etanercept (120). From a clinical point of view, TAILS, compared to other DIL forms, is characterised by a higher frequency of cutaneous manifestations (up to 72% of patients).

Concurrent use of immunosuppressants may reduce the risk of developing autoantibodies and potentially TAILS. Isolated induction of autoantibodies is not an indication for discontinuing therapy. Finally, a few studies investigate if patients can switch to other anti-TNF without recurrence of TAILS: 10 patients who tolerated long-term treatment with similar-acting agents without recurrence of TAILS have been reported in the literature (121).

Anecdotal cases of DIL and flares of preexisting SLE induced by chemotherapy (paclitaxel, capecitabine and doxorubicin) have been described (122-124).

A greater interest is currently being directed towards immune checkpoint inhibitors (ICIs), known to be associated with the risk of developing autoimmune rheumatic manifestations. However, DIL seems a rare event in patients receiving ICIs. In the FDA Adverse Event Reporting System, among 4870 rheumatic events reported with ICIs, only 18 cases of SLE, 7 cases of CLE, 2 cases of lupus-like syndrome and 1 case each for lupus nephritis and central nervous system lupus were identified (125). Only PD1/PDL1 were associated with DIL (mainly nivolumab in 12 cases, followed by pembrolizumab in 4 cases).

Such as idiopathic lupus, DIL can be classified in systemic and cutaneous DIL. Among skin-limited DIL, SCLE has been mostly reported (126), while discoid form of DIL seems to be very rare (127).

In a population-based case-control study of 234 SCLE incident cases in Sweden, 38% could be attributed to drug exposure, with people <50 years at higher risk compared to older ones (126). The highest association was found for terbinafine, followed by anti-TNF. Among anti-hypertensive drugs, ACE-inhibitors resulted associated with SCLE. This study also showed an association between proton pump inhibitors (PPIs) exposure and SCLE, further confirmed in a recent study on the French pharmacovigilance database where, among 60 cases of DIL associated with PPIs, 79.6% were skin-limited (128).

The epidemiology and clinical spectrum of DIL evolve with changes in the pharmacopoeia. Rheumatologists should be aware of this clinical entity, as prompt discontinuation of the causative drug can lead to rapid improvement of clinical manifestations.

Conclusion

Although the exact patterns of SLE onset and disease progression are not fully understood, significant progress has been made over the years in understanding this complex disease. Besides historically known environmental factors, recent advances have been made in deciphering triggers and drivers that contribute to the development of SLE.

In this review we summarised the most recent literature investigating environmental factors potentially involved in the disease onset and clinical expression; despite the big amount of data available, the causal relationship between certain exposures and the disease onset or progression remains frequently elusive and not fully demonstrated. Indeed, epidemiological research on SLE is difficult due to the low prevalence of the disease, its scattered distribution, and the influence of several socio-economic factors on disease expression and evolution. For instance, environmental studies may suffer from serious weaknesses, including the lack of adjustment for individual confounding factors and the inaccuracy in capturing the relevant exposure at the time of disease induction. Thus, environmental-epidemiology studies often lack sufficient power to detect important effects.

Moreover, many environmental-epidemiology studies are cross-sectional. In such designs, the simultaneous assessment of outcome and exposure can give rise to difficulties in determining the temporal aspects of the causal association between exposure and outcome.

Lastly, it is important to note that the available studies refer to a wide range of geographical locations and vary widely in exposure collection methods and SLE phenotypes.

In conclusion, high quality research designs that could help identify the environmental components of the causal pathways leading to SLE and its clinical phenotype are still scarce and should be strongly encouraged.

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