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Review Article

Influence of the environment, gender, and hormones on systemic lupus erythematosus: A narrative review

Sergio Durán-Barragán[a,b], *Juan P. Bátiz-Andrade*[a,b], *Rosal Valenzuela-Marrufo*[b], *Graciela S. Alarcón*[c,d,*]

[a] *Institute for Research in Rheumatology and the Musculoskeletal System (IIRSME), University Center for Health Sciences, Department of Medical Clinics, University of Guadalajara, Guadalajara, Mexico*
[b] *Rheumatology and Obesity Research Clinic S.C., Guadalajara, Mexico*
[c] *Division of Clinical Immunology and Rheumatology, School of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA*
[d] *Department of Medicine, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru*

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ABSTRACT

Systemic lupus erythematosus (SLE) is a multi-systemic inflammatory autoimmune disease whose etiology is incompletely understood. It is thought that certain environmental exposures'trigger' or accelerate the disease in genetically predisposed individuals. The aim of this narrative review is to provide an overview of the latest findings on established environmental factors related to the pathophysiology of SLE and a brief summary of those for which evidence is beginning to be gathered on their role in SLE.

Abbreviations: SLE, systemic lupus erythematosus; GWAS, genome-wide association studies; SNPs, single nucleotide polymorphisms; RR, risk ratio; CI, confidence interval; dsDNA, double-stranded DNA; EBV, Epstein-Bar Virus; HERV, Human Endogenous Retrovirus; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEA, dehydroepiandrosterone; IL, interleukin; TNF, Tumor Necrosis Factor; SLICC, Systemic Lupus International Collaborating Clinics; ACR, American College of Rheumatology; SDI, Systemic Damage Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; ECLAM, European Consensus Lupus Activity Measurement; DAI, Disease Activity Index; OC, oral contraceptive; HRT, hormonal replacement therapy; NHS, Nurses' Health Study; OR, Odds Ratio; DNA, Deoxyribonucleic Acid; RNA, Ribonucleic Acid; UVR, ultraviolet irradiation; UVA, ultraviolet A; UVB, ultraviolet B; IFN, interferon; SPF, sun protection factor; SiO^2, silica; Hg, mercury; HR, Hazard Ratio; VDR, vitamin D receptor; NKT, Natural Killer T; LFA, Lupus Foundation of America; PTSD, Post Traumatic Stress Disorder.

* *Corresponding author.*
E-mail address: galarcon@uab.edu (G.S. Alarcón).

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La influencia del ambiente, el género y las hormonas en el lupus eritematoso sistémico: revisión narrativa de la literatura

Palabras clave:
Lupus eritematoso sistémico
Ambiente
Hormonas
Sexo

RESUMEN

El lupus eritematoso sistémico es una enfermedad autoinmune inflamatoria multisistémica de etiología todavía no claramente dilucidada. Se cree que ciertas exposiciones ambientales pueden desencadenar o acelerar la aparición de la enfermedad en individuos genéticamente predispuestos. Esta revisión narrativa de la literatura aborda los hallazgos más recientes en factores ambientales relacionados con la fisiopatología del lupus eritematoso sistémico y resume brevemente aquellos para los cuales se está comenzando a reunir evidencia sobre su papel en esta enfermedad.

Introduction

Systemic lupus erythematosus (SLE) is a complex multisystemic, chronic autoimmune disease that can affect virtually any organ system of the body. The etiology remains unknown, but it is likely due to loss of immune tolerance to self-antigens and induced autoimmunity in genetically predisposed individuals; this is driven by a complex interplay of defective clearance of apoptotic waste and immune complexes along with neutrophil extracellular traps, sensing of nucleic acids, disrupted lymphocyte biology, and interferon pathways which are triggered by exposure to some environmental factors.

The association of many genes with a predisposition to develop SLE has been clearly established; these genes usually encode for immune components such as *HLA-DRB1*B8, HLA-DRB1*DR3, HLA-DRB1*DR2, IRF5, ITGAM, STAT4, BLK* and *CTLA4,* among others.[1] Genome-wide association studies (GWAS) have identified more than 100[2] single nucleotide polymorphisms (SNPs) that play a role in SLE pathogenesis as well as contribute to disease onset and clinical manifestations.[3,4] Together, they explain the heritability of SLE in up to 47% of the patients and a pairwise concordance rate ranging from 11% to 50% in monozygotic twins.[5–9] The penetration of the disease has been determined in multiple studies. A population-based family study carried out in the Taiwan National Health Insurance Research Database including 23,658,577 individuals, found that having an affected first-degree family member with SLE resulted in an adjusted risk ratio (RR) of 16.92 [95% Confidence Interval (CI) 15.23 to 18.80], while twins of SLE patients have a RR of 315.94 (95% CI 210.66 to 473.82) to develop the disease. Having parents affected had a RR to develop SLE of 14.42 (95% CI 12.45 to 16.70) and siblings of 23.68 (95% CI 20.13 to 27.84).[9] The relatively low penetrance of the disease implies that environmental factors and epigenetic changes play important roles in the etiology of SLE.[10] It is remarkable that in the same study, spouses were found to have a RR of 4.44 (95% CI 2.38 to 8.30) while sharing environmental but not genetic factors. Anti-double-stranded DNA (dsDNA) antibodies are also more frequently present in laboratory workers handling blood from patients with SLE, in comparison with low exposure groups.[11] In another study conducted in Taiwan, a small, but statistically significant higher frequency of lupus in dogs owned by patients with SLE was found.[12] These observations further support the role of an environmental and, possible transmissible factor in the development of SLE.

Some of the established environmental factors involved in the pathophysiology of SLE include hormones and gender, drugs, UV light exposure, and certain viral infections such as Epstein-Bar Virus (EBV), Retrovirus and Human Endogenous Retrovirus (HERV) (Tables 1 and 2).

This monograph will focus on the latest findings on established hormonal, and other environmental factors related to the pathophysiology of SLE.

Methods

We conducted a literature search in PubMed using the following Medical Subject Headings (MeSH) terms “systemic lupus erythematosus” AND “Environment” OR “Hormones” OR “Sex”. Articles in English were considered. No restrictions regarding the date of publication were applied. References of included articles were scrutinized for additional relevant literature.

Epidemiology

Lupus is distributed worldwide with a significant predilection for women of childbearing age with a female to male ratio up to 13:1 in this age group while it is only 2:1 in children and in older individuals.[13–15] SLE is present across ethnicities, but it is more prevalent in non-Caucasians. While prevalence in Europe and United States is higher in people of African descent, SLE is infrequent in Africa[16,17]; this has been called the African gradient for which not a clear explanation has emerged.[18] The Center for Disease Control and Prevention report an estimated prevalence of about 322,000 cases of probable or definite SLE, higher in African Americans, American Indians and Alaska Natives.[15,19,20]

Recent studies have shown that African Americans and US Hispanics also tend to experience worse disease outcomes[21]; however, when socioeconomic factors are considered, the

Table 1 – Established and possible associations with the SLE onset.

Factor	Associations	Possible associations
Hormonal and reproductive factors	• Female sex • High serum levels of estrogens and prolactin • Current use of estrogen oral contraceptives • History of Hormonal Replacement Therapy	• Past use of oral contraceptives • Low progesterone serum levels • Androgen (protective role)
Infectious	• Epstein–Barr Virus primary infection • Human Endogenous Retroviruses • Parvovirus B19	• Cytomegalovirus • Hepatitis C virus • Rubella virus • Dengue virus • Bacterial Agents
Environmental	• Ultraviolet irradiation (exacerbation of preexisting and new cutaneous lesions) • Current but not history of cigarette smoking • Tobacco inhalation • Psychological stress related disorder	• Ultraviolet irradiation • Alcohol consumption (protective role) • Vitamin D deficiency • Microalgae consumption • Vaccinations
Occupational	• Silica exposure	• Mercury

Table 2 – Established and possible associations with SLE flares.

Factor	Associations	Possible associations
Hormonal and reproductive factors	• Prolactin serum elevation	• Oral contraceptives • Hormonal replacement therapy • Pregnancy
Infectious	• Epstein–Barr Virus reactivation	• Cytomegalovirus infection • Group A streptococcus • Vibrio cholerae
Environmental	• Ultraviolet irradiation • Current cigarette smoking • Tobacco inhalation	• Microalgae consumption • Omega-3 Fatty Acids (protective role) • Drugs • Low vitamin D serum levels

variable race/ethnicity is no longer significant in multivariable analysis.[22]

Sex, hormonal, and reproductive factors

While mechanism are not completely understood, epidemiologically, SLE development and severity appear to be influenced by steroid hormones, as 90% of patients with SLE are women, especially during their childbearing years; SLE is also more frequent in men with Klinefelter syndrome (14 times more frequently in comparison with men without SLE).[23] Patients with Klinefelter syndrome exhibit some typical biochemical findings, including low serum total and free testosterone, and high follicle-stimulating hormone (FSH), luteinizing hormone (LH) and serum estradiol concentrations.

Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA), also known as 5-androsten-3b-ol-17-one or diandron,[24] is an important precursor of both estrogens and androgens via peripheral conversion.[25]

Women with SLE tend to have lower levels of androgens, higher estradiol, lower DHEA and DHEA-S (its metabolite), independently of corticosteroid use.[26]

Several randomized clinical trials using DHEA, in women with SLE showed a modest improvement in disease activity along with improvement in bone density.[27,28]

Testosterone

Testosterone is produced in men and women, as this hormone is the immediate precursor of estradiol. Males have a serum concentration about seven to eight times greater than females and it is widely accepted that testosterone has some immunosuppressive effects.[29]

Since women with SLE generally have lower serum testosterone levels, it has been suggested that testosterone might have a protective effect in the onset of SLE.[30–32] In a metanalysis[26] women with SLE were found to have reduced testosterone levels in comparison with controls (eight female-only SLE studies). In contrast, significant testosterone suppression was not found in male SLE patients (4 of 11 male-only SLE studies). Androgens may alter the function of the peripheral immune system by effects exerted during the thymocytes' maturation process, as well as by an increase in

Interleukin (IL) 2 production,[33] a cytokine described to perform abnormally in SLE.[34] It is not known whether the abnormally low androgen status is primary or secondary to abnormal prolactin responses.

While testosterone serum levels could be linked with SLE onset, androgens do not appear to be implied in SLE mortality, as survival rates are comparable in both, women and men with SLE.[35–40]

Estrogens

Estradiol and estrone are the most representative estrogenic hormones and are obtained from the enzymatic aromatization of testosterone and androstenedione, respectively. Estradiol is about ten times more potent than estrone and it is the predominant estrogen in serum.

Because both the onset and exacerbations of SLE have been associated to high serum levels of estradiol, the consumption of oral contraceptives and hormonal changes in the menstrual cycle,[41,42] estrogens are the most obvious and easiest explanation for the gender bias.

Higher serum estradiol levels in SLE female patients in comparison with healthy age-matched controls[43–45] have been shown in numerous studies, although some others have found no significant differences.[46–48] However, a meta-analysis of these studies revealed a significant higher estrogen levels in SLE patients compared with controls in the women-only group, but no significant difference in serum estradiol levels concerning the male-only lupus patients.[26]

The mechanisms involved include estrogen effects on cytokines and B cell function,[33] suppression of lymphocyte production of IL-2,[49] and of Tumor Necrosis Factor (TNF)-alpha,[50] and expression of some HERV mRNA.[51]

Progesterone

Progesterone is an upstream precursor of testosterone and estradiol and has a major role in pregnancy. Its serum concentration is highly variable in non-pregnant women, and the maximum levels are found in the second half of the menstrual cycle (luteal phase) (1.7 to 5.2 ftg/cm^3).[52]

It is recognized that variations in progesterone levels during the menstrual cycle and pregnancy generate reversible changes in the immune system; however, it is not clear whether these changes correlate with an increased risk for autoimmune diseases.[53]

Immunomodulatory phenomena where progesterone is implicated are the modulation of maternal immune response[54] and the suppression of inflammatory response.[55] For the maternal immune system, the fetus is recognized as a semi-allograft, resulting in an upregulation of progesterone receptors on activated lymphocytes amongst placental cells and decidual CD56 + cells. In the setting of pregnancy-progesterone-serum-concentration, immune tolerance is accomplished by these cells, synthesizing a mediator called progesterone induced blocking factor, that affects B cells inducing non-cytotoxic antibodies production, inhibiting NK cells and exerting a synergistic action with prostaglandin E2 and modifying the profile of cytokine secretion by activated lymphocytes: increase in non-inflammatory interleukins production of and reduction of inflammatory cytokines production.[55]

Not many studies have systematically examined serum progesterone levels in adult SLE patients, and to complicate matters further, only one study[56] considered the menstrual cycle variables, showing progesterone to be decreased in the luteal phase in fertile SLE women in comparison with healthy controls. Therefore, evidence is insufficient and contradictory. As an example, an evaluation of 94 female SLE patients (mean age of 29.2 ± 7.0 years) reported that abnormally low progesterone levels were found on half of SLE adult patients (52%).[57] In another study of 128 lupus patients and 96 controls, however, no differences in the serum levels of progesterone between controls and SLE patients with regular menstrual cycles were found; however, progesterone levels were significantly elevated in postmenopausal SLE patients in comparison with their matched controls. (p-value < 0.05).[45]

Some reports on the relationship between progesterone and SLE, and many hormonal reviews may suggest that, if present, progesterone has a minor role in the pathogenesis of SLE. Further research with larger samples would be needed to determine its role with certainty.

Prolactin

Prolactin is a polypeptide hormone secreted by pituitary lactotrophs and inhibited by dopaminergic activity. It can also be produced by other tissues, performing a cytokine role that promotes both cellular and humoral immunity.[58]

High prolactin levels have been observed in 20–30% of SLE patients, specifically in those with active disease.[59] Positive correlation has been found between prolactin levels and some disease activity markers in SLE patients, particularly, anti-dsDNA and anticardiolipin antibodies, erythrocyte sedimentation rate, anemia and hypocomplementemia.[60] Furthermore, low prolactin levels have been linked to remission of the disease.[61] Prolactin appears to precede SLE flares promoting an inflammatory microenvironment,[62] possibly by decreasing the suppressor function exerted by Treg cells over Teff cells.[63] Regardless of patients' risk factors, high prolactin levels have been associated with high disease damage as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI).[64] A meta-analysis including 303 studies, demonstrated a correlation between high prolactin levels and disease activity ascertained with either the SLE Disease Activity Index (SLEDAI), the European Consensus Lupus Activity Measurement (ECLAM), or the Disease Activity Index (DAI).[65]

In epidemiological studies in pregnant SLE patients, where physiological high prolactin levels are found, about 50% of them have an active disease. Furthermore, in a study of 15 pregnant women, high prolactin levels were associated also with lupus anticoagulant positivity, and worse maternal-fetal outcomes.[66]

Oral contraception and hormone replacement therapy

Early age at menarche, oral contraceptive (OC) use, early age at menopause, surgical menopause, and postmenopausal use of hormones have been associated with an increased risk of SLE

as demonstrated in the Nurses' Health Study (NHS) and in the NHSII, which enrolled 121 701 US female nurses in 1976 and 116 430 in 1989, respectively. OC use increased the risk of SLE by 1.5 times (95% CI 1.10 to 2.10). This risk was higher in those patients with less than two years of exposure (RR 1.9, 95% CI 1.30 to 2.8), whereas, paradoxically, for those that had from two to five years of current use, had lower but still significative risk of developing SLE (RR 1.6, 95% CI 1.10 to 2.5).[67]

Past use of OCs has been associated with a marginally increased risk of developing SLE. Compared with never users of OCs, and after adjusting for age and ever use of post-menopausal hormones, the relative risk for past OCs users was 1.40 (95% IC 0.90 to 2.10). No relationship was observed between duration of OCs use or time since first use and the risk of developing SLE.[68]

Current use of OCs containing ethinyl estradiol combined with progestogen has been associated with incident SLE. Higher risk has been found in short-term users (RR 2.52, 95% CI 1.14 to 5.57) in comparison with longer-term current users (RR 1.45, 95% CI 1.06 to 1.99) and increasing with the dose of ethinyl estradiol (RR 1.42, 1.63, and 2.92 for < or = 30, 31–49 and 50 microgram, respectively).[69] Interestingly, in a case–control study, including 545 SLE patients, progestogen preparations provided a protective effect when administered alone (without estrogens) [Odds Ratio (OR) 0.39 in comparison with matched controls, p-value = 0.05].[70]

Hormonal replacement therapy (HRT) also has been linked to an increased risk of developing SLE (Rate Ratio: 1.96; 95% CI: 1.51 to 2.56; p-value <0.001).[71] In the NHS and NHSII cohorts, HRT exposure was also associated with an increased risk of SLE (RR 1.90, 95% CI 1.20 to 3.10). RR was greater if HRT exposure occurred for five years or longer (RR 2.00, 95% CI 1.10 to 3.60) in comparison with shorter exposure, <5 years (RR 1.80, 95% CI 1.00 to 3.00).[67]

Infections

Infections caused by EBV, Parvovirus B19, and HERV have been linked to the pathogenesis of SLE, while data for other infectious agents, such as cytomegalovirus, Hepatitis C virus and some bacterial agents such as vibrio cholera and group A streptococcus, are being gathered at the present time. The data suggest that may all have a role in the pathogenesis of SLE by inducing aberrant innate and adaptative immunity, leading to a loss of tolerance toward autoantigens; however, the associations of cytomegalovirus, Hepatitis C virus, vibrio cholera and group A streptococcus with SLE development have not been yet fully established.[72]

Although many of the mechanisms by which viral agents are involved in the development of SLE remain unknown, there are a few identified mechanisms by which these agents may mediate the pathogenesis of SLE: Molecular mimicry (activation of autoreactive T cells via exogenous antigens with similarities to autoantigens), epitope spreading (the diversification of epitope specificity from the initial focused, dominant epitope-specific immune response), superantigen production by the virus leading to T cells activation with diverse antigenic specificities (due to the lack of the superantigen specificity), bystander activation (where pre-primed T cells are activated by antigen-presenting cells in a high cytokine concentration environment, leading to collateral damage to uninfected neighboring cells and activation of autoimmune responses), persistent viral infection (causing constant immune stimulation and increase of production of autoantibodies and circulating immunocomplexes), and impaired apoptosis and clearance deficiency (resulting in production of antibodies against nuclear structures, via signaling of B cell of the accumulated nuclear material from insufficient clearance of infectious agents and apoptotic cells).[72]

Epstein Bar virus

Epidemiological studies of SLE patients have shown them to have higher rates of EBV seroconversion,[73–75] and particularly against its early antigens in comparison with controls, OR 5.77 (95% CI 2.80 to 11.60 p-value = 0.001)[74,76,77]; these data suggest a recurrent EBV activation.

Mechanisms by which EBV is involved in SLE pathogenesis may include interaction of the following factors[78]: EBV antigens exhibit structural molecular mimicry with common SLE antigens; altered apoptosis and increased B cell signaling led by some of the EBV proteins that have functionality effects in the human immune system; persistent viral infection, as implied by higher viral loads seen in SLE patients; superantigen transactivation (such as *HERV-K18*) by latent EBV infection of B cells, and DNA hypomethylation with increased expression of *HERV-E4*, producing antibodies to endogenous retroviruses, including to protein regions homologous to nuclear antigens,[79–81] and impaired CD8 + cytotoxic T cells and irregular cytokine production in plasmacytoid dendritic cells and CD69 + CD4 + T cells in response to EBV, potentially leading to impaired apoptosis and clearance deficiency.[82–84]

Moreover, studies in children and adults have further supported that EBV infection may be a triggering for SLE onset and flares, as in large cohorts they both appear to be preceded by EBV reactivation.[84,85]

Retroviruses

The association between HERV and SLE has been reported in several studies[80,86–89]; it has been proposed as a molecular bridge between genetic and environmental factors in autoimmune diseases.

Retroviruses are small viruses which replicate only by reversing the normal network of genetic information from DNA to RNA, defined as reverse transcription. Due to mutations of essential genes, some retroviruses have become trapped and integrated into the human genome starting 30–40 million years ago and they have been present in higher primates with the exception of gorillas.[87] These retrovirus-derived elements, denominated HERV, comprise about 8% of human genome[90] and are found in all human cells although they can be differentially expressed. Many HERVs are expressed during embryogenesis and are subsequently epigenetically silenced.[91]

HERVs have the basic structures of infectious retroviruses but, they are transmitted genetically in a classical Mendelian pathway through the germline as proviral DNA[92] in contrast

with exogenous human retroviruses which are infectious have a replication cycle.

Patients with SLE have shown hypomethylation levels of some families of HERVs (*HERV-E, HERV-K*) in their lymphocytes when compared with controls.[88] Some specific HERV implicated in lupus are *HRES-1, HERV-R (ERV-3), HERV-E 4-1, HERV-K10/HERV-K18*.[93]

Factors involved in the HERV hypomethylation and histone deacetylation involve infections, UV exposure, chemicals, stress and hormones such as estradiol.[80] HERV protein expression with molecular and functional mimicry has been documented, whereas accumulated HERV-derived nucleic acids stimulate interferon and anti-DNA antibody production in SLE.[89,93]

The lack of progress in research of HERV and SLE can be explained mainly due to lack of tools to analyze genome-wide, locus-specific expression of proviral autonomous HERV. However, a novel and open-sourced bioinformatics tool called ERVmap, has recently enabled the conduct of a cohort study, in which the RNA sequencing from peripheral blood mononuclear cells obtained from female SLE patients and matched controls was examined. In this cohort, 124 HERVs were clearly identified to be significantly elevated in SLE patients' peripheral blood mononuclear cells compared with healthy controls, but none were repressed. SLE patients expressed higher levels of HERV transcripts as a whole, as well as at the individual locus, and HERV expression largely segregated SLE patients from healthy controls.[94]

Environmental risk factors

Ultraviolet irradiation (UVR)

It has been established that UVR exacerbates pre-existing and new cutaneous lesions, and photosensitivity is one of the classification criteria established by the ACR for SLE. However it remains unclear whether UVR induces the development of the disease.[95] Only a few studies have examined exposure to UVR and the risk of SLE, with potential inaccuracy of exposure assessment and time bias, given that photosensitivity due to SLE can be present well before its diagnosis is made.[96]

UVR strength is influenced by the atmosphere, latitude, altitude, time, and other factors such as the presence of clouding, reflection, and water depth. UVA (320–400 nm), and UVB (290–320 nm) penetrate the earth's ozone layer, while UVC (200–290 nm) is completely blocked. Approximately 10% of UVB reaches the upper dermis, besides 30–50% of visible light and UVA reach the deeper dermis.[97] Experimental studies suggest that UVA and UVB radiation results in induction of reactive oxygen species, increased Interferon (IFN)-alpha in serum, deregulated apoptosis, phagocytic dysfunction, disabling Langerhans cells' function as antigen-presenting cells leading to DNA damage, production of autoantigens and consequently clinical manifestations.[98]

The general recommendation to prevent UVR-induced cutaneous lesions in SLE requires guidance about avoidance of excessive sun exposure, proper sunscreen application and the use of protective clothing. Photoprotective measures have been shown to be beneficial in SLE patients when used properly, including the use of waterproof sunscreen with broad-spectrum protection. These products should be applied every two hours when outdoors, 15 min before sun exposure, and in appropriate amount to cover the exposed skin surface (2 mg/cm^2).[99] An average sized man on a beach vacation would require about 30 mL of sunscreen per day to achieve the target concentration.

Since the relationship between effective Sunscreen Protection Factor (SPF) and the amount of sunscreen applied is nonlinear but logarithmic,[100] using only half of the proper amount (1 mg/cm^2) would provide about only one third of the SPF. Because most people do not apply such a large amount,[101] higher SPF 30 and greater sunscreens or, alternatively, double application. are advised.

Occupational factors and pollutants

Silica and silicates

Silica (SiO^2) is an oxide of silicon that is commonly found in nature as quartz. In occupational settings, where materials containing crystalline silica are reduced to dust (such as mining/tunneling operations), exposure to respirable crystalline silica (<10 μm in size) often occurs. Inhaling crystalline silica dust can lead to silicosis, consisting of deposition of silica particles in the lung alveoli, where they cannot be cleared. This induces an inflammatory response cascade initiated by macrophages; this response eventually leads to pulmonary fibrosis and the nodular lesions characteristic of the disease.[102]

It is unclear whether silica-induced inflammation and fibrosis contribute to the development of autoimmunity.[103] However, inhalation of dust containing crystalline silica is epidemiologically associated with autoimmune diseases. Three population-based, case–control studies with similar methodology have found more SLE patients having a history of silica exposure than their respective controls; in the Southeastern United States[104] (OR 2.10, 95% CI 1.10 to 4.0), in Canada[105] (OR 2.10, 95% CI 1.10 to 3.90) and in African American neighborhoods in Boston[106] (OR 4.30, 95% CI 1.70 to 11.20). The three case–control studies found a dose-dependent-exposure risk.

While some animal model studies suggest that autoimmunity genesis is related to the participation of the innate immune system (leading to proinflammatory cytokine production), and activation of adaptive immunity (induced by pulmonary inflammation), the exact mechanism by which silica is implicated in the break of immune tolerance in SLE remains unknown.[103]

Mercury

Mercury (Hg) is an environmental factor reported to be linked with autoimmunity. Hg is found in dental amalgams, some vaccines, seafood, and some occupational exposure.

In experimental studies, in murine models' exposure to inorganic Hg triggered a lupus-like syndrome. However, evidence in humans appears to be conflicting. While there is no evidence to implicate a role for Hg exposure from dental amalgams in the development or perpetuation of autoimmune disease at the present time, some studies have consistently shown a positive correlation between Hg occupational exposure from gold mining and autoantibody concentrations.

Additionally, there are some reports of individuals with autoimmune disease that have higher concentrations of blood Hg in comparison with healthy controls.

Hg found in its inorganic form, may perpetuate markers of autoimmunity in larger degree than its organic form, although further research is needed to determine its impact on outcomes in humans.[107]

Occupational factors

Epidemiological studies for occupational factors did not find statistical significant association for solvent and pesticides exposure and SLE: OR of 1.0 (95% CI 0.60 to 1.60) and OR of 1.40 (95% CI 0.70 to 2.60), respectively.[106,108]

After the Arizona Department of Health raised concerns about a possible excess prevalence of SLE due to contamination in the area, a case–control study was performed. While higher blood levels of organochlorine and organophosphate pesticides were indeed observed in both controls and cases, no statistical association between elevated levels of pesticides and disease status was found.[109] Another case–control study in North and South Carolina,[108] designed to find out occupational exposure associations, did not find any association between pesticides exposure and SLE either (OR of 0.77, 95% IC 0.34 to 1.80).

Lifestyle and behavioral factors

Cigarette smoking

Strong and specific associations of smoking and SLE risk have been reported suggesting that smoking is involved in SLE pathogenesis. In the NHS and NHSII cohorts, among 286 SLE cases, 45% of women had ever smoked, 51% of whom currently smoked. Compared with never smokers, current smokers had elevated anti-dsDNA antibodies [Hazard Ratio (HR) 1.86, 95% CI 1.14 to 3.04], whereas past smokers did not (HR 1.31, 95% CI 0.85 to 2.00). Women who smoked >10 pack-years (vs. never) had elevated anti-dsDNA antibodies (HR 1.60, 95% CI 1.04 to 2.45) compared with never smokers.[110]

A meta-analysis including nine studies (seven case–control and two cohort studies) revealed an association between current smoking and the development of SLE (OR 1.50, 95% CI 1.09 to 2.08).[111]

Smoker status is an important associated factor for SLE onset; cigarette smokers prior to the onset of SLE have an OR of 6.69 (95% CI 2.59 to 17.28, *p*-value <0.001) while ex-smokers prior to SLE onset have an OR of 3.62 (95% CI 1.22 to 10.70, *p*-value = 0.02)[112]; however, SLE occurrence and former smoking status was not statistically significant (OR 1.39, 95% CI 0.95 to 2.08) in a multivariate Bayesian metanalysis with 3234 individuals who developed SLE and 288,336 control subjects but confirmed the association between SLE occurrence and current smoking status (OR 1.54, 95% CI 1.06 to 2.25).[113]

Tobacco inhalation has also been associated with increased SLE risk, in a case–control study in a Japanese population; those individuals who either inhale at moderate or deep levels had an increased risk of developing SLE (OR 3.73, 95% CI 1.46 to 9.94, OR 3.06, 95% CI 1.81 to 5.15, respectively).[114]

Potential biologic mechanisms linking smoking and SLE risk, include effects upon T and B cells, inflammatory cytokines, oxidative stress, and the formation of short-lived DNA segments.[115]

Cigarette smoking increases the expression of the Fas (CD95) membrane receptor on B and CD4 T lymphocyte cell surfaces,[116] a membrane receptor that transmits signals for apoptosis in lymphocytes, making them more susceptible to apoptotic signals. This potentially induces autoimmunity by overburdening the clearance mechanisms for apoptotic material, which are not intended to handle excessive clearance.

The smoke from cigarettes contains high concentrations of free radicals and can activate endogenous sources of them as well. Both sources are strongly implicated in SLE pathogenesis.[117,118] Free radicals also interact with DNA and cause epigenetic changes as well as mutations.[119] Epigenetic modifications are heritable from one cell cycle to the next, regulate DNA transcription, but do not alter nucleotide sequence and are potentially reversible.[120] As only a small, specific subset of genes need to be expressed in any given human cell, there must be some sort of regulatory system in place to control which genes are exposed and open to transcription, and when. Two of the major mechanisms of epigenetic regulation, methylation and acetylation, are known to be influenced by environmental factors[121] and many epigenetic changes have been described as a result of exposure to cigarette smoke.[122] Thus, it is quite possible that the autoimmune inducing effects of cigarette smoke act via epigenetic modifications, although this has not been well studied or defined to date.

Alcohol consumption

Some studies suggest that moderate alcohol consumption may have a protective effect against the development of SLE, although this is still being debated.[123,124]

A review suggest that a protopathic bias might explain the association: alcohol consumption before SLE diagnosis is not associated with the risk for SLE, and that individuals who develop SLE are more likely to quit.[124]

A systematic review of six case–control studies and a cohort study examining association of pre-diagnosis alcohol consumption with the risk of SLE concluded that there might be a protective role (OR 0.72, 95% CI 0.54 to 0.95) in patients consuming alcohol for <10 years but found no association between moderate alcohol drinking and SLE (OR 0.78, 95% CI 0.49 to 1.24). With a sensitivity analysis excluding one study, the OR resulted to be 0.66 (95% CI 0.49 to 0.89) in the same subgroup.[125]

Nutritional and dietary factors

Vitamin D

While solar UVR may cause SLE disease flares, it is the main source of vitamin D production.[126]

Over the past decades it has been increasingly recognized that vitamin D exerts some impact on the immune system. The roles that vitamin D plays regarding immune activation for combating infection, as well as mediating autoimmune diseases, have been progressively studied. Vitamin D affects immune functions depending on the context of the immune response, in the way that its suppressive or stimulatory action offers physiologically appropriate and immunologically advantageous outcomes.

Vitamin D immunomodulatory properties are mediated by the vitamin D3 receptor (VDR), a member of the nuclear receptor superfamily, in multiple immune cells lineages including monocytes, dendritic cells, and activated T cells.[127]

In vitro, vitamin D exerts an anti-inflammatory and antiproliferative effect by promoting a Th1 to Th2 polarization as well as Th17 to Treg state[128] and also affects the development and function of Natural Killer T (NKT) cells.[129]

Vitamin D deficiency is common in patients with SLE.[130] In patients with lupus, vitamin D deficiency correlates with increased disease activity and fatigue[131] as well as with an increased risk for thrombosis, including from antiphospholipid (aPL) antibodies.[132,133]

Investigations about polymorphisms in the VDR genes and their association with SLE risk have conflicting results. As an example, B allele VDR polymorphisms have been associated with higher risk of SLE in Asian but not in Caucasian populations.[134] Another study using Mendelian randomization analyses of three SNPs (*SSTR4, GC, NADSYN1*) associated with low vitamin D did not support a causal association between them and SLE.[135]

Microalgae

Several in vitro and in vivo studies have shown that *Spirulina platensis, Aphanizomenon flos-aqua, Chlorella, Echinacea,* and alfalfa may release cytokines and chemokines activating the immune system. Case reports suggest the association of ingesting herbs and the clinical onset of auto-immune diseases such as SLE.[136]

Food microalgae including *Spirulina, Aphanizomenon flos-aquae,* and *Chlorella*. are commercialized[137–139] for human use because of their claimed health benefits and possible nutritional value, including reported high protein, vitamin, mineral, and fiber content, and. Numerous animal and human studies have shown that these algae are immune-stimulating[140–153] and it has been reported that these algae can exacerbate, or even precipitate, autoimmune diseases.[154–157]

Spirulina. *Spirulina Platensis* (also known as *Arthrospira platensis*) is a type of blue-green algae with high protein content. It has been called a "super food" in the health food industry due to its supposed health benefits.

Both in vitro and in vivo studies suggest that specific components of *Spirulina* have immune-enhancing effects that are primarily mediated via the innate immune system.[140] Several case reports suggest that Spirulina's immunostimulatory properties can exacerbate, or even precipitate, autoimmune skin disease.[154,155]

Alfalfa. Experiments on rats, rabbits and monkeys suggest that alfalfa or lucerne (*Medicago sativa*), develop immune abnormalities or a lupus-like auto-antibody pattern when fed with it.[158,159]

Monkeys fed alfalfa sprouts developed a lupus-like syndrome, including an erythematous macular rash.[160] In another case report study, four previously healthy individuals who consumed 12 to 24 alfalfa tablets per day for up to seven months developed a symptomatic lupus-like disease, manifested as rash, joint and muscle pains, and positive antinuclear antibodies.[156]

The suspected malefactor in alfalfa is L-canavine, which is an amino acid that is known to replace L-arginine during protein synthesis. As a result, aberrant misfolded proteins are produced that are then ubiquinated and degraded, leading to peptides that can be presented by major histocompatibility complex molecules to CD4 and CD8 cells. These epitopes created by L-canavine may then trigger a cascade of immune events that involve either autoantibody production or cytotoxicity.[153,156]

Given the possible correlation between alfalfa ingestion and disease onset and/or flares, the Lupus Foundation of America (LFA), have recommended avoiding the consumption of alfalfa in patients with SLE.[161]

Vaccinations

Vaccinations have been suggested as possible causes for the development of SLE given their role in stimulating an antigen-specific immune response and production of autoantibodies. Although few reports have suggested the link between SLE and vaccinations,[162,163] these associations have not been confirmed.[164]

Psychological stress

Epidemiological evidence supporting the association between stress-related disorders and autoimmune diseases in humans is limited. However, psychological stress has been linked to a 50% increase risk of developing SLE.[165,166]

A historical cohort study conducted in Sweden, using the National Patient Register included 106,464 patients with stress-related disorders, 1,064,640 matched persons and 126,652 full siblings of these patients. During a mean follow-up of 10 years, the incidence rate of autoimmune diseases was 9.1, 6.0, and 6.5 per 1000 person-years among the stress-related disorders group, matched controls, and sibling cohorts, respectively. Compared with the control population, patients with stress-related disorders were at increased risk of autoimmune disease (HR of 1.36, 95% CI 1.33 to 1.40). The HR for patients with posttraumatic stress disorder were 1.46 (95% CI, 1.32 to 1.61) for any and 2.29 (95% CI, 1.72 to 3.04) for multiple (≥3) autoimmune diseases.[165]

In a US longitudinal cohort of women ($n = 54{,}763$), trauma exposure and posttraumatic stress disorder (PTSD) symptoms were associated with increased SLE risk compared to women with no trauma exposure (HR of 2.94, 95% CI 1.19 to 7.26, p-value <0.05) over 24 years of follow-up.[166]

Conclusions

Significant progress has been made disentangling some clues of the SLE etiology, determining the hormonal and environmental factors whose exposure could lead to the onset or activation of SLE. Female sex and hormonal influence are significant risk factors for SLE. The use of estrogen OC and postmenopausal HRT can cause flares in SLE patients and have been associated with a higher incidence of SLE. Elevated

levels of prolactin are seen in patients with SLE. Several viral infections have been implicated, the underlying mechanism thought to be molecular mimicry. Smoking is also a risk, with a dose-response. Other potential risk factors include silica exposure, vitamin D deficiency, and ingestion of microalgae. Furthermore, development of new bioinformatics tools, such as the ERVmap, should accelerate progress in this race to solve the etiopathogenesis puzzle, and ultimately develop novel and targeted therapies for SLE patients.

Conflict of interests

None declared.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2021.02.008.

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