



## RESEARCH ARTICLE

# Systemic Lupus Erythematosus and implications for the oral cavity

Inês Lopes Cardoso<sup>1\*</sup> | M. Fernanda C. Leal<sup>2</sup> | Renan C. D. Regis<sup>3</sup>

<sup>1</sup>Faculdade de Ciências da Saúde  
Universidade Fernando Pessoa  
Rua Carlos da Maia, 296 4200-150  
Porto Portugal

<sup>2</sup>Health Sciences Faculty,  
University Fernando Pessoa,  
Porto, Portugal

<sup>3</sup>Health Sciences Faculty,  
University Fernando Pessoa,  
Porto, Portugal

### Abstract

Systemic Lupus Erythematosus affects several people around the world and because it is characterized as a chronic inflammatory disease of multifactorial origin, and with systemic impairment, great attention must be paid from diagnosis to treatment in order to optimize the entire follow-up of the patient.

The dental doctor plays an important role in the diagnosis of the condition and must be attentive to the early signs that can appear in the oral cavity with a frequency of up to 21%.

In this way, through this bibliographic review, which has as main goal to correlate Systemic Lupus Erythematosus with its direct consequences in the oral cavity, it will be possible to help dentists in the diagnosis, to understand in detail the development of the disease and what attitude should be taken in its presence.

Keywords: Lupus Erythematosus, Systemic Lupus Erythematosus, Oral manifestations

## 1 | INTRODUCTION:

Systemic Lupus Erythematosus (SLE) is an autoimmune, multisystemic and chronic inflammatory disease of the connective tissue, characterized by the production of antibodies against various cellular constituents. The disease can lead to a wide variety of signs and symptoms, and there may be periods of exacerbation with recurrences and remissions depending on the individual, the therapeutic management, and other unknown factors (1,2).

SLE has several clinical manifestations, which may affect one or more organs and systems. In this pathology, the immune complex no longer recognizes the cell antigens, which leads to a deficiency in the regulatory mechanisms and leads the antibodies to act

against the organism itself, causing hypersensitivity reactions, injuries, inflammation and pain (3).

Despite the advances made over the years, little is known about the etiology of the disease. This pathology is more common in women under reproductive age and may be associated with other autoimmune

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**Corresponding Author:** *Inês Lopes Cardoso*  
*Faculdade de Ciências da Saúde Universidade Fernando Pessoa Rua Carlos da Maia, 296 4200-150 Porto Portugal*  
*Email: [mic@ufp.edu.pt](mailto:mic@ufp.edu.pt)*

diseases, being its development affected by environmental factors and genetic predispositions (2,3). In the scientific world, this fact can be observed by the greater involvement of monozygotic twins, when compared to the dizygotic twins (2).

SLE patients are affected by a variety of orofacial disorders. These oral manifestations are moderately frequent, affect 9 to 45% of patients and may be the first signs of disease or systemic changes related to a specific treatment (1,4). The most affected areas are the tongue, cheek mucosa, lips and palate, being the most common acute ulcerations and/or erythema (2), as well as angular cheilitis, mucositis, glossitis, discoid lesions and white lines that resemble oral lichen planus (1).

There seems to be a possible association between periodontal disease and SLE. Periodontitis can vary in severity regardless of the degree of bacterial infection, thus suggesting that dysregulation of the host's inflammatory response can be considered a trigger for the evolution of the autoimmune disease (5).

SLE patients may also show other oral manifestations such as diseases in the salivary glands, dry mouth, and temporomandibular disorders (4). Consequently, these patients need special oral care, due to their susceptibility to infections (2).

Thus, the goal of this study was to conduct a literature review focusing on the relevant aspects related to the recognition of oral manifestations of the disease and systemic conditions, in order to offer health professionals a deeper knowledge on the subject.

## 2 | MATERIALS AND METHODS:

To carry out this bibliographic review, the online databases PubMed, Scielo and Lilacs were used, and the keywords found to better describe the theme were Lupus Erythematosus; Systemic Lupus Erythematosus; Oral Manifestations. The selection criterion was based on the use of considerably recent scientific articles and the old ones were selected according to their relevance to the subject addressed.

## 3 | CHARACTERIZATION:

Lupus erythematosus can be divided into discoid lupus erythematosus (DLE), limited to erythematous patches on the patient's skin, and systemic lupus erythematosus (SLE), the most recurrent, that affects several organs and systems of the body (skin, kidneys, heart, lungs, bloodstream and joints).

SLE is a chronic autoimmune disease of inflammatory origin with several clinical manifestations, including in the oral cavity. Among the most well-known general signs and symptoms are those that manifest mainly in the skin (80% of the time, as is the case of the butterfly-shaped rash), in musculoskeletal tissues and at the hematological and serological level. According to the American College of Rheumatology (ACR), the presence of SLE characteristics in the oral mucosa, such as ulcers, is considered one of the criteria for diagnosing the disease (6,7).

SLE manifests itself in different ways because it is a multisystem disease. For this reason, diagnosis requires special attention to be correctly determined. According to the ACR, 11 criteria must be used to facilitate the diagnosis of SLE. These are malar and discoid rashes, photosensitivity, oral ulcers, non-erosive arthritis, pleuritis or pericarditis, renal, neurological, hematologic and immune impairments, and presence of antinuclear antibodies. When 4 of these criteria are present, there is a high probability of being SLE (6).

According to Albilal et al. (8) some of the most common symptoms in this disease are fatigue, malaise, arthralgia (when the inflammatory condition becomes known as arthritis), myalgia and mucocutaneous lesions. Although arthralgia is the earliest manifestation of SLE, musculoskeletal involvement seems to be the predominant symptom in the disease, as well as the development of generalized skin rashes, induced by sunlight and discoid lesions secondary to epithelial atrophy with subsequent healing. One of the most striking features of the skin rashes observed is the shape of a butterfly symmetrically located in the malar and back of the nose (8). A recent study points out for the divergence of cutaneous lupus manifestations that may present in a single

patient over a period of time (9). This indicates the importance of a clinical-pathological correlation for the correct diagnostic of this condition and for the choice of the adequate therapeutic approach.

Studies indicate that SLE has a prevalence of 30 to 50 cases per 100,000 inhabitants and its incidence ranges from 0.9 to 3.1% per 100,000 inhabitants per year. Women between 30 and 40 years of age are the most affected, with a 10:1 ratio to men (8,10).

#### 4 | ETIOLOGY:

The development of the pathology is based on an exaggerated inflammatory process with vascular changes that involve vasculopathy and deposition of immune complexes. These immunocomplexes are often composed of IgG and IgM and eventually IgE and lead to a generalized or organ-specific type III hypersensitivity reaction (8,11).

An important immunological data that defines the pathogenesis of SLE is the production of autoantibodies that end up acting directly on one or more proteins of the individual, characterizing what is popularly known as an autoimmune disease. The production of autoantibodies causes tissue damage promoted by an inflammatory response mediated by the previously mentioned immunocomplexes (12).

There is strong evidence that the development of SLE has genetic influences such as polymorphic genes, however, there are also factors of environmental origin that can influence the predisposition of individuals to the appearance of this condition. Among these factors are infections (mainly by the Epstein-Barr virus), excessive sun exposure and the use of certain medications such as hydralazine, procainamide, phenytoin, and isoniazid (8).

##### 3.1. Genetic factors

Although the etiopathogenesis of SLE is still unknown, research indicates that genetic, hormonal, and environmental factors are related to the development of immunological abnormalities that characterize this disease (13).

The evidence of genetic susceptibility associated with the development of SLE is the 10-fold increase

in the occurrence of the disease in monozygotic twins when compared to dizygotic twins, in addition to the presence of autoantibodies and cellular changes in the relatives of patients (13-16).

Studies suggest that the most common genetic changes associated with SLE are those found at the main histocompatibility complex *locus* (MHC or HLA). The predisposing *loci* are *HLA-DR2* and *HLA-DR3* and these gene regions encompass several genes whose interactions are complex and vary in different ethnic groups. Thus, the *HLA-DRB1*, *HLA-DRB1\*0301* and *HLA-DRB1\*1501* *loci* have been associated with the development of SLE, while *HLA-DRB1\*1401* reduces the risk of this disease (13,17).

Factors of genetic vulnerability to the development of SLE are the combination of the presence of susceptibility genes with the absence of protective genes such as the *TLR5* polymorphisms or the genetic variant with loss of function of the tyrosine phosphatase protein, non-receptor, type 22 (PTPN22) (13).

A recent study identified a novel susceptibility gene to SLE (18). These researchers were able to conclude that the allele rs2582511 of the gene *PLD4*, coding for phospholipase D4 is associated with anti-dsDNA antibody production, leading to autoimmune phenotypes compatible with SLE, including splenomegaly and lymphadenopathy (18).

##### 3.2. Environmental factors

Some environmental factors may be related to the development of SLE. One of the most discussed in the literature is the influence of the Epstein-Barr virus (EBV) on the development of the condition. This is due not only to the fact that high proportions of anti-EBV antibodies have been found in patients with SLE, but also to the finding that EBV infection precedes the autoimmune changes seen in SLE (2).

In addition to EBV, SLE can be induced by some drugs, with procainamide being responsible for most cases. When the drug influence is confirmed in the diagnosis, it is possible to verify the presence of anti-histone antibodies. In clinical terms, some thromboembolic consequences can also be observed. In these cases, the great advantage is the possibility of the disappearance of the condition by interrupting the

use of the medication (19).

Vitamin D deficiency, exposure to silica and tobacco consumption have also been identified as environmental factors involved in the development of SLE, since they reduce tolerance to autoantigens. In the case of vitamin D, patients with SLE show extremely low levels of this vitamin. The influence of silica, present mainly in materials used in restoration work, has been confirmed in several case-control studies with patients exposed to this substance. Finally, tobacco also seems to influence the development of this disease, especially during the appearance of skin lesions (20,21).

Other factors such as exposure to metals, pesticides and pollutants and even cosmetics may be related to SLE, however, despite the evidence of their association with SLE, further studies are necessary due to the divergence of results presented in different researches (21).

## 5 | ORAL MANIFESTATIONS:

Systemic autoimmune diseases often present oral changes in their early stages of development. SLE is included in this group, which facilitates early diagnosis and intervention. Oral manifestations appear with a frequency of 6.5 to 21% of SLE cases, being the most affected regions the cheek mucosa, tongue, lips, and palate. The lower lip region may show fissures, bleeding and edema (22).

Although some cases of this pathology do not present a precise symptomology, in cases with oral lesions, it is mainly observed well-defined chronic ulcerated areas or with an erythematous aspect. These areas vary in size and are characterized by having the center in the form of whitish papules surrounded by streaks also of white color. Its appearance involves periods of remission and crises (7,10).

### 5.1. Gingivitis and periodontal disease

One of the implications of SLE is the development of gingival inflammation (gingivitis) and periodontal disease that directly affect the support and support structures of the teeth. The most common types of

gingivitis are scaly gingivitis and marginal gingivitis, which have a strong relationship with the accumulation of plaque that is retained by the gingival tissue. This plaque results from the poor oral hygiene of patients with SLE, associated with discomfort in the oral cavity, which ends up discouraging or hindering their hygiene, resulting in the formation of dental calculus plates (8).

In turn, periodontal disease, despite having a different etiology from SLE, seems to have some similarity with autoimmune disease regarding the mechanism of action. Both occur due to dysregulation of the affected individual's innate immune system, with involvement of cytokine gene polymorphisms such as interleukin 10 (IL-10), tumor necrosis factor (TNF) and IgG Fc receptor in both conditions (2).

Calderaro et al. (23) evaluated the severity of the periodontal condition in patients with and without SLE, in samples of the same gender, age, socioeconomic and cultural level, suggesting that there is no difference in the periodontal condition. According to these authors, in patients with SLE, periodontal disease manifested earlier than in healthy controls, suggesting the need for strict periodontal monitoring of patients with this pathology.

Umbelino Junior et al. (2) suggested that SLE patients need more care with oral diseases. It was observed an index of periodontal pockets and bleeding 18% higher than the general population and it has also been reported that the presence of SLE can influence the progression of these diseases due to its inflammatory character and its susceptibility to infectious agents. It is emphasized that further studies are needed to prove this assumption.

However, Mutlu et al. (24) observed that SLE patients had smaller periodontal pockets when compared to the control group. These authors suggested that these observations may be related to the possibility that the patients examined are under prolonged therapy with immunosuppressants, corticosteroids and non-steroidal anti-inflammatory drugs.

Still other studies have shown that patients with SLE had plaque indices like individuals without this condition (23). In another study, greater depth of periodontal pockets was observed in individuals with SLE when compared to healthy individuals (24).

It is important to note that SLE, being an inflammatory disease, can aggravate patients' periodontal conditions and consequently contribute to greater tooth loss (5,25).

As can be concluded from the studies presented, there are controversies regarding the possible association between SLE and periodontal disease. However, it is recommended that patients with this autoimmune disease undergo periodic follow-up (23).

### **5.2. Hyposalivation and xerostomia**

The sensation of decreased amount of saliva (xerostomia) and hyposalivation are conditions that occur frequently in cases of SLE, as a result of the use of certain medications such as non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants that can considerably affect the amount and quality of saliva produced (11,26).

This dysfunction of the salivary glands can also occur due to chronic inflammation resulting from autoimmune disease. Studies demonstrate an association of SLE with another autoimmune disease, Sjögren's syndrome, which affects the salivary glands and generates glandular involvement in a similar way to what occurs in SLE (11,26).

Gilboe et al. (27) found a prevalence of xerostomia in 37% of SLE cases. This symptomology was more common in these patients when compared to healthy people or patients with rheumatoid arthritis.

As a result of the reduction in saliva production, patients are predisposed to the development of dental caries, periodontal disease, non-infectious pharyngitis and to the appearance of ulcers. In addition, it is possible to verify the onset of mucositis that compromises the ingestion and swallowing of food and promotes a reduction in the quality of oral hygiene (8).

The salivary decrease that leads to low lubrication, also compromises daily activities such as eating, which can lead to dysphagia (difficulty in swallowing) and dysgeusia (taste change) (28).

### **5.3. Temporomandibular joint disorders**

Arthritis and arthralgia (joint pain) are common in patients with SLE, and the involvement of the temporomandibular joint (TMJ) may also be present, reported in 60% of cases (6).

TMJ disorders are a consequence of ligament laxity, increased contractures, and muscle atrophy. The literature states that patients undergoing immunosuppressive therapy for the treatment of SLE are most affected by TMJ disorders in their different degrees of severity, which may include limited mouth opening and changes in laterality (1,6,26).

TMJ dysfunctions have been reported in 41% of SLE patients, being proven by radiographic changes in 30% of cases. Among these changes, the most observed were flattening and erosion of the mandibular condyle. Studies have suggested an association between TMJ deformations and other joints (4,29).

### **5.4. Ulcers and recurrent aphthous stomatitis**

Mainly located in the gingiva, oral mucosa, redness of the mouth and palate, ulcers together with the burning sensation are characteristics of high incidence in patients with SLE, varying between 7 and 41% according to recent literature (10). These lesions can start as petechiae and evolve into ulcerated lesions that can present painful symptoms (10,11,30).

The ulcers commonly present in SLE, when they become chronic, pose a risk of malignant transformation to squamous cell carcinoma. Therefore, it is recommended to perform biopsies and repeat them when the diagnosis is uncertain or the lesions appear to have no improvement, so that the treatment is carried out as soon as possible (7,22).

Recurrent aphthous stomatitis (RAS) is also a common sign of SLE and can be seen in the early stages of the disease, thus being a sign of great relevance for early diagnosis. It should be noted that pediatric patients with DLE and mucosal involvement, including RAS lesions, are more likely to make the transition to SLE (22).

## **6 | DIAGNOSIS:**

The diagnosis of SLE is clinical, anatomopathological and serological. When symptoms already exist, the diagnosis becomes essential, since the prognosis depends on the early treatment of the disease (19).

The markers of this disease are the anti-nucleosome antibodies (autoantibody against the chromatin constituent nucleosomes), anti-native DNA (antibody

characteristic of SLE patients), anti-Sm (autoantibody specific to SLE) and anti-Ro (antibody against the Ro antigen which can be found in SLE, Sjogren's Syndrome or Rheumatoid Arthritis) (31).

The diagnostic importance is in the presence of DNAN as an antigen (called native or double helix DNA) that leads to the production of an anti-DNA autoantibody, present in 70% to 80% of patients with the disease. Anti-DNAN antibodies are found almost exclusively in SLE patients and are therefore considered to be markers of this disease. The most used tests for its detection are those of indirect immunofluorescence, which have less sensitivity, but great specificity for SLE, and ELISA that allows the detection of less specific antibodies and greater sensitivity at the expense of specificity (32).

For the correct diagnosis to be made, a detailed intraoral clinical examination is of great importance. Care when assessing the oral cavity allows for better planning for choosing an appropriate treatment, with consequent risk reduction and favorable prognosis. However, despite the relevance of this stage, many dentists end up not prioritizing it and the results can lead to a compromised patient's health (26).

Although the oral manifestations of SLE have quite striking characteristics, there are some other conditions that can be confused with this pathology. The differential diagnosis includes lichen planus, erythema multiforme, traumatic lesions, leukoplakia, candidiasis, lichenoid reactions to metal restorations (amalgam) or drugs (beta-blockers or non-steroidal anti-inflammatory drugs) and other vesicle-bullous lesions (7,8).

In addition to the importance of correct diagnosis, it is necessary to warn that studies have shown an increase in squamous cell carcinoma in chronic ulcerous lesions in patients with SLE, which reaffirms the need for a detailed intraoral examination (7,8).

In the diagnosis of a recurrent aphthous ulceration (RAU), it is important to assess the association of the oral manifestation with a systemic disease. This diagnosis must be made through a detailed anamnesis and blood tests such as complete blood count and assessment of vitamin B12, iron and folate deficiency. If the dentist is unsure of the diagnosis, a biopsy may be necessary. Some authors claim that

with the definitive diagnosis of RAU without painful symptoms, treatment is not necessary (33-35).

## 7 | TREATMENT:

According to the American Academy of Dermatology, the main recommendations for the treatment of SLE with mucocutaneous manifestations are to avoid sun exposure and if you do so, wear protective clothing or photoprotectors with minimal UVB-15 protection; use of topic corticosteroids; systemic therapies that include first-line antimalarial drugs, aminoquinoline, dapsone and prednisolone (12).

The treatment of lupus erythematosus, in its two forms (discoid and systemic), begins with general measures such as counseling, support and guidance for patients and their families, as well as multidisciplinary treatment. In addition, treatment should be supplemented with dietary guidance for the prevention and control of osteoporosis, obesity, and systemic arterial hypertension. Protective measures against sunlight and other forms of ultraviolet radiation are required using topical photoprotectors and physical barriers such as long-sleeved clothing and the use of a hat.

The use of medications for the treatment of SLE may explain the lack of conclusive results in attempts to correlate oral and skin manifestations with the prognosis of the disease (36), as these alter the mucosa, making it difficult to determine the etiology of oral lesions in these individuals (37,38). Scully (34) created an organization chart that facilitates the follow-up of the treatment of SLE, which must be done in a multidisciplinary way and associated with some medications depending on the systemic involvement of the disease.

Patients with SLE and the presence of mouth ulcers and gingivitis are treated effectively with topic corticosteroid medications. However, according to research, the continuous contact of the medication with the lesion surface in the oral mucosa is more difficult to be achieved, being, in these cases, necessary to prescribe aerosol medications. It is also useful to use antimalarials to control oral lesions (29,37). Some authors have observed fungal infections in SLE pa-

tients, mainly during immunosuppressive therapy and/or during the exacerbation of the disease (39).

SLE patients should be instructed to use soft toothbrushes and fluoride products due to the potential to reduce acidity, dental caries, and possible infections. In addition, it is important to warn patients of the extreme importance of avoiding foods with spices and/or peppers, as well as acidic fruits, as they can aggravate ulcers and other lesions present and generate even more discomfort (26).

Some authors consider it necessary to perform panoramic X-rays of the TMJ, as a form of control, to assess possible bone changes in this structure (11,40).

## 8 | DISCUSSION:

Lupus erythematosus is an autoimmune disease characterized by chronic inflammation, the etiology of which is still poorly understood. SLE is an autoimmune, chronic inflammatory, multisystemic and complex disease. This pathology evolves with polymorphic clinical manifestations, with periods of exacerbation and remission. According to several studies, environmental factors, genetic predispositions, and the use of some medications are related to the development of this disease (1,41).

The correct diagnosis and control of autoimmune disease requires a multidisciplinary medical team, including the dentist (22,42). SLE patients are affected by a variety of oral changes. The literature is still scarce on this subject and it is difficult to make it evident that there is any association between systemic disease and oral alterations. The manifestations present in the oral cavity vary according to the severity of the disease. According to Mustafa et al. (43), oral lesions, when present, are usually multiple and distributed asymmetrically, and may be asymptomatic in 50% of patients.

The literature presents a lower frequency of reports on oral lesions in patients with SLE, compared to reports describing skin lesions. This fact can be explained by the lack of incidence of ultraviolet radiation in the oral cavity in contrast to the skin (36). According to Louis & Fernandes (19), the oral regions

most affected by SLE are those of the vestibular mucosa, gums and lips due to the susceptibility to the development of cheilitis, although lupus can affect any surface of the oral mucosa.

The lesions can manifest as erosion in the mucosa, ulcers surrounded by an irradiated striated pattern, flaking surface plaques and fissures with hemorrhagic tendency, incidence of ulcerations, erythema and keratosis, present on the tongue, cheek mucosa, gums and hard palate, resulting from tissue damage caused by immune complex-mediated vasculopathy. In addition, several studies report the risk of possible malignancy of some oral ulcers (2,8,44,45).

Regarding the age group, SLE has a predilection for women of childbearing age in the second and third decades of life and may be associated with other autoimmune diseases (2,3,10,31). It can also affect other ages, both sexes, with all races being affected, although the disease is more severe in the black race (46-48).

In the study by Umbelino Junior et al. (2), in which the incidence of oral manifestations in SLE was assessed, a prevalence of oral lesions of 6.5% was observed, hairy leukoplakia in 3.7% and candidiasis in 20.0% of SLE cases. Although there is a frequency of oral lesions in SLE, overall, the specific prevalence of oral manifestations in females is low (47,49).

There are few reports in the literature associating SLE with periodontal disease. Studies have shown a potential association between these two pathologies, indicating that dysregulation of the host's inflammatory response has an influence on disease progression (5,50,51).

Several studies claim that the involvement of salivary glands in SLE is associated with the presence of secondary Sjögren's syndrome (8,52,53). However, other studies report patients with xerostomia without an association between the two pathologies (27,54).

The therapeutic choice for SLE is individualized and depends on the symptomatic manifestations and the severity of the disease. However, it is a consensus that all patients with SLE should start treatment with drug therapy unless there is an evident contraindication (55).

Due to the variability of orofacial disorders that affect patients with SLE including oral lesions, non-specific ulcerations, involvement of salivary glands and TMJ problems, it is important that the dentist is attentive to the signs and symptoms of the oral condition that can serve for the diagnosis early SLE.

## 9 | CONCLUSION:

Despite the innumerable advances in knowledge about the functioning of the immune system in normal and pathological conditions, more studies are needed to be able to act in its prevention, or at least in an earlier diagnosis.

Since SLE affects the oral cavity, it is important that the dentist knows how to assess, diagnose, and treat oral changes, aiming at a local and systemic improvement. The dentist, in agreement with a multidisciplinary team, must be aware of drug interactions and surgical interventions to improve oral health to avoid systemic complications. In this way, it will be possible to develop more effective therapies with less adverse effects that enable the remission of the disease and provide quality of life to patients.

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