Periodontitis is associated with higher subclinical atherosclerosis in patients with systemic lupus erythematosus

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Abstract

Aim: To determine periodontitis prevalence in patients with systemic lupus erythematosus (SLE) and to assess whether periodontitis in SLE patients is associated with a greater subclinical atherosclerosis.

Methods: An observational case–control study was conducted in SLE (cases) and patients without any rheumatic diseases (controls), matched for sex. Sociodemographic and cardiometabolic variables were gathered, and SLE activity was assessed through several indexes. Periodontal examination registered probing pocket depth, clinical attachment level, bleeding on probing, plaque index, and tooth loss. Subclinical atherosclerosis was assessed by measuring the carotid–femoral pulse wave velocity (PWV) by Doppler velocimetry, homocysteine levels, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Bivariate analyses and logistic regression were used to assess the association of any of the studied variables with SLE.

Results: Seventy-one cases and 72 controls were included in the study. Thirty-nine SLE patients (54.9%) were diagnosed with periodontitis, compared with 16 controls (22.2%). High levels of PWV (≥7.7 m/s, 75th percentile) were shown by 44.3% of the cases vs. 22.4% of the controls (p = .011). Among SLE patients, those with periodontitis showed higher PWV values (8.1 ± 1.52 vs. 7.16 ± 1.11 m/s, p = .006) and higher homeostasis model assessment index (indicative of insulin resistance) (1.7 ± 0.73 vs. 2.92 ± 3.05, p = .028) compared to those with periodontal health. Logistic regression showed that waist circumference (OR 1.06, 95% CI 1.01–1.12, p = .015); ESR (OR 1.09, 95% CI 1.03–1.16, p = .003); and bleeding on probing (OR 1.1, 95% CI 1.01–1.19, p = .018) were associated with the risk of SLE.

Conclusion: Systemic lupus erythematosus patients showed a higher periodontitis percentage than controls. Higher PWV values were found in SLE patients with periodontitis, indicating a higher prevalence of subclinical atherosclerosis. Patients with higher gingival bleeding showed a higher risk of SLE.

Keywords
atherosclerosis, cardiovascular diseases, lupus erythematosus, systemic, periodontitis, pulse wave analysis

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1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototype of a systemic autoimmune disorder characterized by inflammation, which mainly affects women of reproductive age. Early diagnosis and the improvement of the available treatments have led to a greater survival of these patients, mainly through a good control of infections and SLE outbreaks. Cardiovascular disease (CVD) is currently the leading cause of death, in the period beginning 5 years after initial diagnosis, due to the high prevalence of atherosclerosis and faster atherosclerosis progression among SLE patients. A good cardiovascular risk assessment is necessary in order to achieve lower CVD mortality in SLE patients.

Periodontitis is an inflammatory disease, associated with and probably caused by a multifaceted dynamic interaction among dysbiotic biofilm, host immune responses, hazardous environmental exposure, and genetic propensity. A controversial two-way relationship has been proposed between periodontitis and SLE, and the reported rates of periodontitis in SLE patients have been compared to the ones found between periodontitis and type 2 diabetes mellitus. The use of systemic immunosuppressive drugs in patients with SLE may contribute to an earlier manifestation of periodontitis. Periodontitis, on the other side, would aggravate SLE-related cardiovascular complications such as endothelial dysfunction and atherosclerosis. Two meta-analyses on the relationship between periodontitis and SLE reported contradictory results. One meta-analysis performed on four studies reported a risk of periodontitis in SLE cases compared with controls significantly greater, with a risk ratio of 1.76, but no differences were found in clinical periodontal parameters, like probing pocket depth (PPD) or clinical attachment loss. The other metaanalysis showed a significant association between periodontitis and SLE (OR 5.32), and SLE patients presented higher bleeding on probing (BOP) and higher mean clinical attachment loss compared with controls.

Scientific evidence has widely linked periodontitis with a higher incidence and prevalence of CVD and specifically with acute myocardial infarction. Marfil-Álvarez et al. demonstrated that severe and extensive periodontitis led to more severe acute myocardial infarction. This relationship has been recently explained in two meta-analyses by atherosclerosis. A higher atherosclerotic process has been found in patients with periodontitis, measured by pulse wave velocity (PWV). PWV is the gold standard and the most validated noninvasive method for the assessment of arterial stiffness. Endothelial damage and inflammation are one of the first steps in CVD development, and many novel biomarkers related to those initial steps have been investigated. Homocysteine has been proposed as a disruptor of the endothelial function, leading to vessel damage, atherosclerosis progression and, ultimately, to CVD. Maintained high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are other biomarkers associated with atherosclerosis and CVD predictors.

Our study hypothesis is that patients with SLE have a higher risk of presenting periodontitis. Also, patients with SLE and periodontitis present more CVD affections due to an aggravated atherosclerotic process. The objectives of our study were to determine the prevalence of periodontitis in patients with SLE and assess whether the diagnosis of periodontitis in SLE patients is associated with a more severe atherosclerotic process, measured by PWV, ESR, and CRP, and also determine whether periodontitis or any periodontal clinical variable could be considered as risk factors for SLE.

2 | PATIENTS AND METHODS

2.1 | Participants

An observational case–control study was conducted on patients from the Autoimmune Diseases Unit at the University Hospital Virgen de la Nieves in Granada (Spain). Cases were patients with SLE consecutively attended at the service. SLE diagnosis was considered if the patient met ≥4 of the 11 criteria from the American College of Rheumatology, as revised in 2019. Control subjects without SLE, matched for sex, were recruited from hospital staff, relatives of hospitalized patients, and staff from different companies. Exclusion criteria for SLE patients were as follows: impaired mental state, pregnancy or breastfeeding, previous periodontal treatment, antibiotic therapy in the last 3 months, and <1 year of follow-up. The exclusion criteria for control group were as follows: impaired mental state, pregnancy or breastfeeding, SLE or any other systemic disease, previous periodontal treatment, antibiotic therapy in the last 3 months, and corticosteroid therapy. Approval was obtained from the Hospital biomedical ethics committee (CEIH Granada ref. 0843-N-21). Written informed consent was signed by each patient at the enrollment. Patients were treated in accordance with the Helsinki Declaration, following its last revision of 2013. STROBE guidelines were followed for the preparation of the present manuscript.

2.2 | Variables

Sociodemographic and cardiometabolic variables were gathered from each participant in both groups: sex, age, higher education level, waist circumference (cm), smoking habit, menopausal status, and sedentary lifestyle according to the level of daily physical activity (no physical activity or less than 30 min/day). CVD diagnosis was considered positive when subjects presented at least one of the following parameters in their medical record: coronary heart disease (acute myocardial infarction or angina), valvular heart disease, chronic heart failure, or a cerebrovascular accident. A family history of premature CVD was defined as the presence of a first-degree relative who had experienced an acute myocardial infarction or cerebrovascular accident before the age of 55 in men or 65 in women. Blood pressure was measured twice using a calibrated automatic device (HEM-7051T, Omrom Health Care). Patients were considered hypertensive when systolic blood pressure (SBP) was higher than 140 mmHg or diastolic blood pressure (DBP) was higher than 90 mmHg. Carotid–femoral
PWV was measured by Doppler velocimetry (Complior-Analyse, ALAM-MEDICAL). The cutoff values for PWV were established as the 75th percentile of the control group. Cardiovascular risk score was determined using the Framingham criteria. Treatment with statins, antihypertensive drugs, immunosuppressants, and hydroxychloroquine was also registered in all participants.

SLE Disease Activity Index (SLEDAI)\(^{18}\) and the Systemic Lupus International Collaboration Clinics (SLICC)\(^ {19}\) indexes were used to measure SLE activity and cumulative organ damage.

All oral and periodontal clinical examinations were performed by a single periodontal and calibrated specialist (R.M.-A.). An interexaminer agreement of 80% was obtained for the agreement between R.M.-A. and the reference researcher (F.M.) in a sample of 10 patients. A variability of ±1 mm in the measurement of PPD was accepted. A calibrated PCPUNC15 periodontal probe (Hu-Friedy) was used to determine the PPD and the clinical attachment loss (CAL) in six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) except in the case of third molars and teeth that were rehabilitated with crowns or dental implants. Periodontitis case definition was made according to the criteria of the EFP periodontal definition and classification.\(^3\) Periodontitis extension was measured using the Arbes index, calculated as the percentage of sites with CAL ≥3 mm, and periodontitis severity was assessed using PIRIM index (PIRIM = \(\sum (d_i/n)_t\)), where “i” is the site, “d” is the PPD of the site in mm, “n” is the frequency of the sites, and “t” is the number of remaining teeth. BOP was determined as the percentage of bleeding teeth, following the criteria by Ainamo and Bay.\(^{21}\) The presence of plaque was registered scored using plaque disclosing tablets according to plaque index by O'Leary.\(^{22}\)

At the same appointment or in morning next to it, blood samples were gathered from each participant to determine biochemical and immunological parameters. Total cholesterol (mg/dl), HDL-cholesterol (mg/dl), LDL-cholesterol (mg/dl), and triglycerides (mg/dl) were assessed, as well as fasting blood glucose (mg/dl). C-reactive protein (mg/dl), ESR (mm/h), uric acid (mg/dl), homocysteine (µmol/L), and insulin (µU/ml) levels were assessed. Homeostasis Model Assessment (HOMA) index for insulin resistance was calculated.\(^{23}\) All samples were processed, and all laboratory tests were performed at the clinical analysis laboratory of the “Virgen de las Nieves” University Hospital in Granada (Spain).

### 2.3 Statistical analysis

A conservative sample size calculation was made, taking into account that the prevalence of periodontitis according to recent evidence in general population is 35%, and in patients with SLE is 60%. The prevalence of periodontitis in SLE patients presented a wide range of values in publications from the last 6 years, going from the 35% of Wu et al. in 2017,\(^ {24}\) and the 89% of Fabbri et al. in 2014.\(^ {25}\) Taking these values into account, and in order to achieve a statistical power of 85%, necessary to detect differences in the null hypothesis test H0: \(p_1 = p_2\), using a bilateral Chi-squared test for two independent samples with a significance threshold of 5%, A minimum of 71 patients would be needed in each group, making a total of 142 subjects in the study.

Normality testing of the study variables was performed using the Shapiro–Wilk test. A bivariate analysis was performed to identify those variables associated with SLE in the study participants applying Chi-squared test, Fisher’s exact test, Student’s t test, and Mann–Whitney’s U-test based on each variable’s characteristics. A multivariate logistic regression model was implemented, with SLE/control as the dependent variable, using a stepwise approach. Only independent variables with statistical significance \(p < .20\) in the bivariate analysis and \(p > .10\) selection criteria were taken into account for the model. The odds ratio and confidence interval were calculated at 95% confidence. A 5% significance threshold was used for all variables. All the analyses were performed with the same statistical software package (SPSS Statistics 19 for MAC IOS, IBM).

### 3 RESULTS

Seventy-one patients with SLE and 72 control subjects were enrolled in the study from January to December of 2015, and there were no losses to follow-up during the study (Figure S1). All participants were Caucasians. Regarding disease duration in SLE patients, the average duration was 13 years. Most patients presented with stable disease (SLEDAI score 2). Organ damage index was also low (SLICC score 0.7). The frequency of lupus-related complications such as nephritis, neurological, hematological or articular manifestations, and serositis was 43.7%, 9.9%, 42.3%, 93%, and 28.2%, respectively. 13% of patients tested positive for antiphospholipid antibodies. Regarding drug therapy, 58.6% were being treated with prednisone and 93% with hydroxychloroquine. The average daily dose of prednisone was 3.35 mg/day, and the cumulative prednisone dose was 1.4 g. A 35.2% of patients were being treated with immunosuppressive drugs: 26.8% with mycophenolate, 9.9% with methotrexate, 5.6% with azathioprine, and 4.2% with cyclophosphamide.

Demographic and cardiometabolic characteristics are shown in Table 1. In both groups, there was a similar percentage of women (95.8%). SLE patients were significantly older than control subjects (39.8 vs. 33.9 years old, respectively, \(p = .002\)), and presented higher levels of triglycerides, homocysteine, ESR, insulin, HOMA index, and PWV compared with controls. After considering the PWV cutoff at the 75th percentile of our sample, being 7.7 the threshold value, the percentage of SLE patients with PWV ≥7.7 was almost double compared with the percentage of controls (44.3% vs. 22.4%; \(p = .011\)). In comparison with SLE patients, control subjects presented lower waist circumference, higher levels of physical activity, and higher percentage of participants with higher education (university).

Table 2 shows that all periodontal clinical variables were worse in patients with SLE compared with controls, with the exception of plaque index. Following the case definition of periodontitis of the EFP 2018, 39 out of 71 (54.9%) of the SLE patients were diagnosed with periodontitis (\(p < .001\)). Regarding the staging within the patients
with periodontitis of the SLE group, 1 (2.56%) presented a stage I, 13 (33.33%) presented a stage II, 13 (33.33%) presented a stage III, and 12 (30.77%) presented a stage IV. The grading of the periodontal patients of the SLE group was grade B for 30 (76.92%) and grade C for 9 (23.08%) patients. The periodontal patients of the control group presented the following periodontitis staging: 0 (0%) presented stage I, 3 (18.75%) presented a stage II, 5 (31.25%) presented a stage III, and 8 (50%) presented a stage IV. The grading of the periodontal patients of the control group was grade B for 10 (62.5%) and grade C for 7 (43.75%) patients. 

The grading of the periodontal group of patients of the control group was grade B for 10 (62.5%) and grade C for 7 (43.75%) patients. Table 3 shows the comparison of clinical variables between the subgroups of SLE patients with and without periodontitis. SLE patients with periodontitis presented higher
insulin resistance according to HOMA index (p = .028) and higher PWV (p = .006). Other atherosclerosis biomarkers were higher in the periodontitis subgroup (homocysteine, ESR, and CRP), but the differences did not reach statistical significance. The presence of CVD and Framingham CVR score was also higher in this subgroup, although differences were not statistically significant. Table 4 shows the results of the multivariate model, with SLE/control as dependent variable, with the OR of the variables that showed association with a higher risk of presenting SLE. Of all periodontal variables, only a high BoP was associated with a higher risk of presenting SLE (OR = 1.102, p = .018).

### 4 | DISCUSSION

The carotid–femoral PWV is a measure of subclinical atherosclerosis and the gold standard for determining arterial stiffness. In our study, this variable was statistically significantly higher in SLE patients with periodontitis (1 point higher) compared with SLE patients without periodontitis. As shown by Vlachopoulos et al., a difference of 1 m/s in PWV leads to an increased risk (adjusted for age, sex, and risk factors) of 14% for cardiovascular events and 15% for cardiovascular mortality and overall mortality.

Blood pressure at the time of registration is key to establishing PWV; the elastic modulus of the arteries changes depending on whether the pressure is normal or elevated. As described in the Materials & Methods section, all patients in the study had their blood pressure measured, as shown in Table 3. The mean of both blood pressure values was within normality in both subgroups of SLE patients (taking into account that 37.7% of SLE patients were in therapy with antihypertensive drugs). Age is another biological factor that modifies PWV, although the age between both subgroups was also different (42 vs. 36 without periodontitis); our results show that the periodontitis subgroup presented a mean PWV value one point higher than the optimal PWV value for their age group in healthy people, while the mean value in the subgroup without periodontitis was 0.5 points higher than the ideal one for their age range.

Among the biomarkers associated with atherosclerosis, homocysteine levels showed higher levels in the group of SLE patients with periodontitis, and their values were above normality (the normal concentration range of homocysteine in blood is 5 to 12 µmol/L). Although it is a very novel biomarker, these values were not statistically different from SLE patients without periodontitis. ESR and CRP values showed similar results. These could be explained by the fact that both ESR and CRP are biomarkers of systemic inflammation and 60% of SLE patients were treated with daily prednisone, and 93% with hydroxychloroquine, both of them anti-inflammatory drugs. Also, other therapies like immunosuppressants, such as azathioprine, have an anti-inflammatory effect. Insulin levels and HOMA index of peripheral insulin resistance were much higher in this subgroup (SLE and periodontitis). It is known that systemic inflammation causes insulin resistance due to the effect of insulin on its cellular IRS receptor. Cytokines such as TNF-α, IL-6, and IL-1β, (very common in periodontal inflammatory processes) could contribute to insulin resistance through multiple mechanisms, such as the activation of Ser/Thr kinases, the decrease in the expression of IRS-1 receptor, glucose transporter type 4 and peroxisome proliferator-activated receptor gamma, or the expression and activation of the suppressor of cytokine signaling-3.

We can deduce that a state of chronic inflammation associated with periodontitis in SLE patients, aside from known cardiovascular risk factors, could explain an increased prevalence of subclinical atherosclerosis. Therefore, periodontitis could be considered an emerging cardiovascular risk factors and may explain the increased prevalence of cardiovascular disease in SLE patients.

Eleven observational analytic studies, 2 meta-analyses, and a randomized controlled trial have been published since year 1993 until present date on the association between periodontitis and SLE. The range of prevalence of periodontitis in SLE patients is very wide in these publications, with values up to 89%. Our study confirms a higher percentage of periodontitis, greater periodontitis extension according to Arbes index, periodontitis severity assessed through PIRIM index, and higher BoP in patients SLE compared with controls. Thirty-nine out of 71 SLE patients (54.9%) were diagnosed with periodontitis according to the case definition of the EFP 2018. Although they were patients prescribed with daily anti-inflammatory therapy, which could affect periodontal clinical parameters, the impact of immunosuppressive therapy on SLE patients may be greater.

### Table 2. Periodontal clinical variables of the study participants (n = 143)

| Variable                          | Controls (n = 72) | SLE (n = 71) | p-Value  |
|-----------------------------------|------------------|--------------|----------|
| Periodontitis, n (%)              | 16 (22.2%)       | 39 (54.9%)   | <.001a   |
| Probing pocket depth 4–6 mm, mean ± SD | 1.42 ± 5.08     | 4.89 ± 10.40 | <.001b   |
| Probing pocket depth >6 mm, mean ± SD | 0               | 0.29 ± 1.94  | .039b    |
| PIRIM Index, mean ± SD            | 0.25 ± 0.89      | 1.08 ± 3.13  | <.001b   |
| Arbes Index, mean ± SD            | 0.031 ± 0.073    | 0.11 ± 0.17  | <.001b   |
| Missing teeth, mean ± SD          | 1.56 ± 2.44      | 3.80 ± 5.66  | .001b    |
| Bleeding on probing (%), mean ± SD| 3.59 ± 7.34      | 9.95 ± 13.75 | .001b    |
| Plaque Index (%), mean ± SD       | 9.99 ± 6.86      | 9.67 ± 8.62  | .806c    |

aChi-squared test.
bMann-Whitney’s U-test.
cStudent’s t test.
Immunosuppressors in SLE patients would affect the systemic immune dysregulation of several immune cell types, including macrophages, neutrophils, CD4+ T cells, and dendritic cells and imbalance between pro-inflammatory and anti-inflammatory cytokines. This immune dysregulation could also contribute to a dysbiosis of the subgingival microbiota, which would explain the higher prevalence of periodontitis in SLE patients. A higher proportion of *Candida albicans*, *Aggregatibacter*
actinomycetemcomitans, Tannerella forsythia, and Treponema denticola have been found in juvenile SLE patients and active periodontal sites of patients with SLE, in comparison with healthy controls.32 On the contrary, SLE-related immune complexes have been detected in gingival biopsies of SLE patients submitted to periodontal surgical treatment, and the intake of low-dose immunomodulators was associated with lower accumulation of immune complexes and improved periodontal outcomes.33

The two metanalyses published to date found a statistically significant increased risk of periodontitis in SLE patients compared with controls, with a risk ratio of 1.76 (95% CI 1.29–2.41),7 odds ratio = 5.32, 95% CI 1.69–16.78.8 Rutter-Locher et al.7 report no differences in periodontal clinical parameters, while Zhong et al.8 found differences in some of them, between SLE patients and controls. Our results showed differences in periodontal clinical parameters between SLE patients and healthy controls (see Table 2), except in the plaque index. The differences found between the studies included in the two previous metanalyses may be due to a difference in the periodontitis case definition and the clinical measurement of periodontitis, the dosage of anti-inflammatory and immunosuppressive drugs, and the clinical study design (sample size, type of study). Bae et al. performed a Mendelian randomization study on the association of periodontitis with rheumatoid arthritis and SLE. Their results showed a significant association between periodontitis and SLE, concluding that there is a causal relationship between periodontitis and SLE and that propose periodontitis as a prelude of these autoimmune diseases rather than a consequence.34

We explored a different way that could be plausible in a bidirectional relationship between SLE and periodontitis, as proposed by other authors. Wang et al. found that Treponema denticola and Porphyromonas gingivalis and the combination of both in patients with SLE was associated with increased titers of anti-β2-glycoprotein I and anti-cardiolipin antibodies.35 Porphyromonas gingivalis-specific genotypes fimA-Ib, fimA-II, and fimA-IV, the ones more associated with periodontitis, were found as the most prevalent ones in SLE patients compared with controls.36

Aggregatibacter actinomycetemcomitans is also a bacterial species known to be a trigger of the autoimmune response in diseases such as SLE and rheumatoid arthritis.7

Of the three independent variables that showed to be risk factors for SLE in our study (waist circumference, ESR, and BoP), according to the results of the adjusted logistic regression model, BoP is the variable that showed the greater OR (1.102) for suffering SLE. In a recently published randomized clinical trial, the authors reported that periodontitis treatment improved the response to immunosuppressive therapy in SLE patients. This result, however, must be considered with caution, since the patients of the study were diagnosed with periodontitis using only the bleeding gingival index as criterion. The mean PPD was 1.7 mm in the group of treated patients, and the sample size and duration of the study were very short (32 patients during 3 months).25

A limitation of our study is that SLE patients were, on average, older than controls (40 years vs. 34 years), which could have affected the prevalence of periodontitis; however, we think that the age group where it occurs the difference does not affect this frequency measurement. Another potential limitation is that the SLE group could not be representative of general SLE patients from a Caucasian population, due to a selection bias, but the demographic characteristics of this group are similar to the ones of other previously published studies with larger samples.6,37,38

Our study, the second largest in the European population, provides the information that periodontitis is a treatable factor, so early intervention can prevent at least to a certain extent the development of an atherosclerotic process that constitutes the basis of future cardiovascular events in patients with SLE.

5 | CONCLUSION

In this case–control study, periodontitis was more common in patients with SLE compared with controls. PWV is higher in patients with SLE with periodontitis, which indicates a higher percentage of subclinical atherosclerosis. Gingival BOP was the only modifiable periodontal variable that was associated 1.102 times with suffering SLE.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.