Periodontal findings in systemic lupus erythematosus patients and healthy controls

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ABSTRACT

الأهداف: مقارنة الحالة الصحية للثة في عينة من المرضى المصابين بالذئبة الحمراء الجهازية، وعينة مجموعة التحكم من الاشخاص الأصحاء؛ بالإضافة إلى تحديد ما إذا كان هناك علاقة بين مؤشرات صحة اللثة والمؤشرات الحيوية للذئبة الحمراء.

الطريقة: أُجريت هذه الدراسة المقطعية في كلية طب الأسنان، جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من نوفمبر 2012م إلى فبراير 2014م. شملت الدراسة 25 من المرضى المصابين بالذئبة الحمراء (مجموعة الدراسة) و50 من الأشخاص الأصحاء (مجموعة التحكم). وقد اعتمد تقييم اللثة على كل من: عمق الجيب اللثوي، ومستوى الارتباط اللثوي، ونزيف اللثة، ومقدار البلاك. فيما تم تسجيل مجموعة من نتائج الاختبارات المعملية لدى مجموعة الذئبة الحمراء وهي كالتالي: عدد خلايا الدم البيضاء، ومستوى الهيموجلوبين، وعدد الصفائح، والأجسام المضادة للنواة، ومضاد الحمض النووي، ومستوى الكالسيوم، وفيتامين د.

النتائج: أشارت نتائج الدراسة إلى عدم وجود اختلاف واضح من الناحية الإحصائية في صحة اللثة بين المرضى المصابين بالذئبة الحمراء وعينة مجموعة التحكم. وقد كان مرضى الذئبة الحمراء الذين لم يتعرضوا لانتكاسات المرض لأكثر من عام أكثر عرضة لنزيف اللثة ووجود الجيوب اللثوية العميقة مقارنةً مع أولئك الذين تعرضوا لانتكاسات خلال أقل من عام قبل بدء الدراسة. وكان مستوى الارتباط اللثوي لدى مرضى الذئبة الحمراء المصابين بأعراض التهاب المفاصل أعلى مقارنةً بالذين ليس لديهم التهاب في المفاصل. ولم توجد علاقة واضحة من الناحية الإحصائية بين علامات صحة اللثة والمؤشرات الحيوية للذئبة الحمراء.

الخاتمة: أظهرت الدراسة بأن لا يوجد اختلاف في صحة اللثة بين مرضى الذئبة الحمراء والأشخاص الأصحاء. بينما عند مرضى الذئبة الحمراء وجد أن حدة التهابات اللثه كان لها علاقة بعاملين هما: تكرر إنتكاس المرض ووجود أعراض إلتهابات المفاصل.

Objectives: To compare periodontal findings in systemic lupus erythematosus (SLE) patients and healthy controls, and to determine, whether there is a correlation between periodontal parameters and SLE biomarkers.

Methods: This cross-sectional study was conducted in the Faculty of Dentistry, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia between November 2012 and February 2014. Twenty-five participants diagnosed with SLE and 50 healthy controls were selected. Periodontal assessment consisted of clinical attachment level (CAL), probing depth (PD), bleeding on probing, and plaque scores. For the SLE group, several laboratory tests were obtained, such as, white blood cell count, hemoglobin level, platelet count, anti-nuclear antibody, anti-double-stranded DNA antibody, calcium level, and vitamin D.

Results: Periodontal findings in SLE patients and controls were not significantly different. The SLE patients who had no flare-ups for more than a year showed significant bleeding on probing and deeper PD compared with those who had flare-ups less than a year before starting the study. The SLE patients with arthritis symptoms showed more CAL than those without arthritis. In the SLE patients, no significant correlation was found between their periodontal findings and SLE biomarkers.

Conclusion: Periodontal health was not different between SLE patients and healthy controls. In SLE patients however, flare-ups and presence of arthritis had a significant relation with periodontal health.

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Periodontitis is a common chronic infectious disease that affects most adults. In the Kingdom of Saudi Arabia (KSA), recent data suggests a prevalence of 68%.[1] Periodontitis is characterized by chronic gingival inflammation that leads to destruction of the periodontal tissues supporting the teeth, and subsequently, may lead to tooth loss. Although it is primarily initiated by bacteria, the host immune response plays a significant role in its development.[2-4] Recently, there has been an increasing interest in the relationship between periodontitis and systemic health. Several studies[5-8] have suggested an association between periodontitis and systemic autoimmune diseases, such as rheumatoid arthritis. Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disorder of unknown etiology that has a similar pathobiology to periodontitis. It is characterized by B-cell hyperactivity with an increased immunoglobulin (Ig) G production, and immune complex deposition that results in connective tissue damage.[9] In KSA, the prevalence of SLE in the population was reported to be 19.3 in 100,000, with a female to male ratio of 9.8:1.[10,11] Current monitoring strategy for SLE patients depends on laboratory testing for acute phase markers and autoimmune serology. Acute phase markers consist of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which may help to distinguish between lupus flare-ups and infection.[12] Autoimmune serology may include anti-double-stranded DNA (anti-dsDNA) antibodies, anti-nuclear antibodies (ANA), and complement (C)3 and C4 levels.[13] Anti-dsDNA antibodies are disease markers, and potential predictive markers for flare-ups. It has been found to be positive in 80.1% of cases, and was also found to positively correlate with disease activity, and has shown a capacity to predict future flare-ups.[11,14-18] The ANA test is a very sensitive test for diagnosing SLE, but it is not specific as it can also be positive in some chronic infections.[19] Periodontitis and SLE are both multifactorial conditions that share several pathogenic characteristics, such as elevated serum levels of beta 2-glycoprotein I-dependent anti-cardiolipin, the IgG Fc receptor, and proinflammatory cytokines.[20,21] However, limited and inconsistent data are present on the association between SLE and periodontitis.[22-24] Furthermore, no study has assessed if there is a correlation between the severity of periodontitis and SLE biomarkers. This study was conducted to compare the periodontal findings in SLE patients and systemically healthy controls, and to determine whether there is a correlation between periodontal parameters and SLE biomarkers.

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Methods. This cross-sectional study was conducted from November 2012 to February 2014 in the Faculty of Dentistry, King Abdulaziz University, Jeddah, KSA. This study was reviewed and approved by the Research Ethics Committee of the Faculty of Dentistry, King Abdulaziz University, and was conducted in accordance with the principles of the Helsinki Declaration. Informed consent was obtained from each participant prior to their enrollment. Inclusion criteria for the test group was female subjects with a confirmed diagnoses of SLE, and who were 20 years of age, or older. Exclusion criteria were smoking, pregnancy, diabetes, history of periodontal treatment in the preceding 6 months, and those with systemic conditions requiring antibiotic prophylaxis prior to periodontal examination. For the control group, similar inclusion, and exclusion criteria were employed except for the lack of SLE history. Twenty-five patients diagnosed with SLE according to the classification criteria of the American College of Rheumatology[25] were recruited from the Rheumatology Clinic at King Abdulaziz University Hospital. A control group consisting of 50 individuals without history of SLE, or other autoimmune diseases were randomly selected from patients presenting for treatment at the dental clinics of King Abdulaziz University, Faculty of Dentistry.

Data collection. Sociodemographic data and full periodontal assessments were collected from all subjects. Periodontal assessments consisted of the following: probing depth (PD); clinical attachment level (CAL); plaque index (PI); bleeding on probing (BOP); and the number of teeth present. Three calibrated examiners performed the periodontal assessment. Intra-examiner repeatability was 91%, and inter-examiner repeatability was 89% for recording the PD within one mm. In SLE patients, the following data were gathered from their medical records: time of SLE diagnosis; last activity of the disease; kidney involvement; hospital admission; and medications used. The following laboratory tests were also recorded: white blood cell count (WBC); hemoglobin level (HB); platelet count (PLT); ANA; anti-ds-DNA antibody; calcium level; urine protein; and vitamin D (Vit D).

Statistical analysis. Data was tabulated and analyzed using the Statistical Package for Social Sciences statistics for Windows version 20 (IBM Corp, Armonk, NY, USA). The results were shown as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess for normality assumption. Comparisons between SLE and healthy controls for age and gingival bleeding, an independent sample t test was performed, and for other variables, the Mann-Whitney U test was used. Correlations between laboratory investigations and clinical periodontal parameters were determined by Pearson correlation analysis. In the SLE group, clinical periodontal parameters were compared between subjects with, and without arthritis symptom, recent flare-ups, and nephritis using the Mann-Whitney U tests. $P<0.05$ was considered significant.

Results. A total of 75 female subjects (25 SLE patients and 50 healthy controls) were included in this study. As shown in **Table 1**, the mean age was 33 years for SLE subjects, and 37 for the control group with no statistically significant difference between the groups ($p=0.186$). Although the periodontal status was generally worse for SLE compared with the controls, there were no significant differences between the 2 groups. The mean percentage of pockets ≥5 mm was higher in SLE (11.3%) compared with the controls (5.6%), however, the difference was not statistically significant between the 2 groups ($p=0.788$). Similarly, the mean sites with clinical attachment loss of ≥2 mm were 75.8% for the SLE group, whereas it was 71.9% for the control group ($p=0.314$). The correlations between laboratory investigation in SLE patients and percentage of pocket ≥5 mm, and CAL ≥2 mm in SLE group are shown in **Table 2**. None of the laboratory tests were found to be significantly correlated to a pocket ≥5 mm, or CAL ≥2 mm. **Table 3** shows the comparisons of periodontal parameters in patients with SLE who had flare-ups within the last year, and those who were stable for more than one year. The mean PD was 2.26 ± 0.47 in those who had recent flare-ups compared with 3.09 ± 1.42 mm who were stable for more than one year ($p=0.066$). The percentage of deeper pocket (≥5 mm) was significantly higher among those who had recent flare-ups compared with those who were stable for more than a year ($p=0.032$). The percentage of bleeding sites was also significantly higher among those with recent flare-ups ($p=0.046$). **Table 4** shows the comparisons of periodontal parameters in patients with SLE who presented, with or without arthritis. The mean PD was 2.48 ± 0.53 mm in those who had arthritis compared with 2.55 ± 1.06 mm among those who

Table 1 - Comparison of clinical parameters between systemic lupus erythematosus (SLE) and control groups included in a study on periodontal findings.

Variables	SLE (n=25)	Control (n=50)	*P*-value*
Age, year	33.32 ± 9.12	36.73 ± 11.00	0.186
PD, mm	2.62 ± 1.06	2.44 ± 0.64	0.862
CAL, mm	3.14 ± 2.91	2.42 ± 1.00	0.381
Plaque, %	77.52 ± 24.31	80.37 ± 21.58	0.833
Bleeding, %	63.36 ± 22.27	56.01 ± 23.89	0.202
Number of teeth	23.20 ± 4.68	23.61 ± 3.99	0.932
PD ≥5 mm, %	11.34 ± 27.28	5.58 ± 10.45	0.788
CAL ≥2 mm, %	75.77 ± 24.89	71.87 ± 24.08	0.314

Values expressed in mean ± standard deviation. PD - probing depth, CAL - clinical attachment level. *independent sample t test was used for age and gingival bleeding, and the Mann-Whitney U test was used for the other variables

Table 2 - Correlation of laboratory tests with pocket ≥5 mm and clinical attachment level (CAL) ≥2 mm in systemic lupus erythematosus patients from Saudi Arabia.

Laboratory test	Mean ± SD, n=25	Pocket ≥5 mm, %		CAL ≥2 mm, %	
		Correlation	*P*-value	Correlation	*P*-value
WBC	5.91 ± 3.54	-0.186	0.491	0.110	0.684
HB	11.65 ± 1.46	0.014	0.958	0.323	0.223
PLT	283.68 ± 154.36	-0.122	0.652	-0.087	0.750
ANA	900.00 ± 466.93	-0.479	0.061	0.346	0.189
Anti-dsDNA	424.78 ± 454.16	-0.161	0.551	0.141	0.602
Vitamin D	34.71 ± 16.90	-0.027	0.923	0.070	0.805
CRP	7.47 ± 7.07	-0.067	0.806	0.056	0.838
ESR	25.26 ± 18.33	-0.389	0.152	0.111	0.693
C3	0.89 ± 0.19	-0.101	0.731	-0.221	0.447

WBC - white blood cell count, HB - hemoglobin level, PLT - platelet count, ANA - anti-nuclear antibodies, Anti-dsDNA - anti-double-stranded DNA, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, C - complement

Table 3 - Clinical periodontal parameters and flare-ups in systemic lupus erythematosus patients from Saudi Arabia.

Variables	Flare-ups		*P*-value
	<one year (n=14)	≥one year (n=11)	
Plaque, %	73.66 ± 27.50	82.44 ± 19.69	0.537
Bleeding, %	55.30 ± 18.36	73.62 ± 23.34	0.046
Number of teeth	24.64 ± 3.87	21.36 ± 5.14	0.073
PD, mm	2.26 ± 0.47	3.09 ± 1.42	0.066
PD ≥5 mm,%	2.09 ± 3.43	23.11 ± 38.71	0.032
CAL, mm	2.43 ± 0.66	4.04 ± 4.27	0.298
CAL ≥2 mm, %	79.87 ± 18.31	70.56 ± 31.57	0.622

Values expressed in mean ± SD. PD - probing depth, CAL - clinical attachment level

Table 4 - Clinical periodontal parameters and arthritis in systemic lupus erythematosus patients from Saudi Arabia.

Variables	Arthritis		*P*-value
	Yes, n=13	No, n=12	
Plaque, %	83.90 ± 15.46	79.11 ± 30.22	0.940
Bleeding, %	64.52 ± 22.35	50.80 ± 22.83	0.057
Number of teeth	22.33 ± 4.67	24.46 ± 3.57	0.120
PD, mm	2.48 ± 0.53	2.55 ± 1.06	0.371
PD ≥5 mm, %	9.47 ± 24.86	6.47 ± 20.96	0.053
CAL, mm	2.75 ± 0.44	2.66 ± 3.10	0.002
CAL ≥2 mm, %	78.27 ± 27.37	66.49 ± 23.31	0.021

Values expressed in mean ± standard deviation. PD - probing depth, CAL - clinical attachment level

Table 5 - Comparison of clinical parameters between systemic lupus erythematosus, with and without lupus nephritis patients from Saudi Arabia.

Variables	Nephritis		*P*-value
	Yes, n=6	No, n=19	
Plaque, %	80.02 ± 13.38	76.73 ± 27.12	0.896
Bleeding, %	63.11 ± 27.30	63.44 ± 21.31	0.799
Number of teeth	22.00 ± 4.60	23.58 ± 4.76	0.337
PD, mm	2.91 ± 2.02	2.54 ± 0.59	0.408
PD ≥5 mm, %	17.90 ± 39.71	9.27 ± 23.14	0.746
CAL, mm	2.77 ± 0.89	3.26 ± 3.32	0.975
CAL ≥2 mm, %	80.85 ± 17.50	74.17 ± 27.01	0.899

Values expressed in mean ± SD. PD - probing depth, CAL - clinical attachment level

had none (p=0.371). The percentage of deeper pocket (≥5 mm) was higher among those who had arthritis compared with those who had none (p=0.053). The mean CAL (p=0.002) and percentage of CAL ≥2 mm were significantly higher among those with arthritis (p=0.021). In the SLE group, periodontal condition of patients with and without history of lupus nephritis was compared as shown in **Table 5**. The percentage of sites with ≥5 mm PD was 17.90 ± 39.71 mm among those with nephritis, whereas it was only 9.27 ± 23.14 mm among those without nephritis; the difference however, was not statistically significant.

Discussion. The relationship between periodontal diseases and inflammatory conditions and diseases, such as, diabetes and cardiovascular disease are well established.[26-29] An SLE and periodontitis are both inflammatory diseases involving several components of the immune system. B-lymphocytes play an important role in both SLE and periodontal disease. In addition, IgG2 was shown to be the predominant IgG subclass in subjects with SLE and periodontitis.[30] Periodontal disease is suggested to have a strong autoimmune component, which continuously stimulates interest in exploring the relationship between periodontal and autoimmune diseases.[2] Studies on the effect of SLE on periodontitis are limited and inconclusive. There are case reports showing aggressive periodontitis in systemic and cutaneous SLE patients.[22,23]

In the present study, there was no difference in periodontal parameters between SLE patients and healthy controls, suggesting that there is no effect of SLE on the prevalence of periodontal disease. An earlier study showed that SLE patients had significantly reduced periodontal PD compared with healthy individuals, which could be attributed to the fact that these patients are on anti-inflammatory medications.[24] It has also been shown that SLE patient had lower cytokine level in their gingival sulcular fluid. A study examining cytokine levels in SLE patients found that although the plasma level of interleukin-1 beta (IL1-β) and interleukin-18 (IL-18) are increased with SLE, these cytokines are decreased in gingival sulcular fluid, and this was accompanied with no difference in the gingival bleeding index between the SLE group and healthy controls.[31] The SLE patients are prescribed several medications, depending on their clinical conditions, such as steroids, immunosuppressive, and antimalarial drugs. These drugs have been shown to decrease the inflammatory process, which is a key element in periodontal tissue destruction. In addition, the dosage is increased when SLE patients experience flare-ups. Immunosuppressive agents, such as methotrexate, azathioprine, and mycophenolate mofetil are frequently considered in patients who are non-responsive, or unable to reduce steroids below doses that are acceptable for chronic use.[32] In the present study, patients who suffered from flare-ups within the last year had less deep pockets than those who were stable for more than one year, suggesting that the increased dose of medication possibly contributed to controlling periodontal inflammation.

Genetic pleomorphism is a very important factor in both SLE and periodontal disease. In fact, a relationship has been found between both diseases in certain genotypes.[21,33] The present study did not explore genetic variations between subjects, which might be another explanation for the lack of difference in periodontal parameters between SLE and healthy controls. The presence of periodontal disease has been shown to affect the management of SLE and rheumatoid arthritis.[5,6,8,34] Moreover, periodontal treatment was shown to improve the SLE activity of patients on immunosuppressive

medication.[34] In the present study, SLE patients with arthritis had higher CAL and deeper pockets compared with patients without arthritis. This may suggest that there is a decrease in response to SLE therapy due to active periodontal disease, or the increased severity of periodontal disease had contributed to the presence of arthritis.

This is a cross-sectional study with several confounding factors, and hence, a cause and effect relationship cannot be established, and this limits our study. Systemic lupus erythematosus is a rare condition with a prevalence of less than 2 per 10,000 person, hence, the sample size of the current study was not large. In future studies, it is preferable to select incidence cases of SLE patients to reduce possible confounding factors by medications and SLE duration.

In conclusion, there were no differences in periodontal parameters between patients with SLE and systemically healthy individuals. Also, no significant correlation was found between SLE biomarkers and periodontal parameters. This similarity might be due to anti-inflammatory medication taken by SLE patients, and/or possible lack of genetic variation. Within SLE patients, those who suffer from arthritis had more periodontal tissue destruction compared with those without arthritis. Further studies are needed to verify the results of this study.

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