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ORIGINAL ARTICLE

Periodontitis in patients with systemic lupus erythematosus: A nationwide study of 1,990 patients

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Abstract

Background: The aim of this study was to examine the association between systemic lupus erythematosus (SLE) and periodontitis in Norway during a 10-year period from 2008 through 2017.

Methods: In this population-based study, 1,990 patients were included in the SLE-cohort based on diagnostic codes registered in the Norwegian Patient Registry. The control group (n = 170,332) comprised patients registered with diagnostic codes for non-osteoporotic fractures or hip or knee replacement because of osteoarthritis. The outcome was periodontitis, defined by procedure codes registered in the Control and Payment of Health Refunds database. Logistic regression analyses were performed to estimate odds ratio for periodontitis in patients versus controls adjusted for potential covariates.

Results: Periodontitis was significantly more common in SLE patients compared to controls (OR 1.78, 95% CI 1.47-2.14) and the difference was highest in SLE-patients 20 to 30 years of age (OR 3.24, 95% CI 1.23 – 8.52). The periodontitis rate in SLE patients was in the same range as for patients with diabetes mellitus type 2.

Conclusions: Patients with SLE had an almost doubled risk of periodontitis compared with the control population, and the difference was most accentuated in the young patients. These findings warrant an increased focus on dental health in SLE-patients.

KEYWORDS
Systemic lupus erythematosus, registries, epidemiology, periodontal diseases, inflammation, autoimmune diseases

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic, autoimmune chronic inflammatory condition with diverse clinical manifestations, primarily affecting joints, internal organs, skin and oral mucosa[1–4] The etiology of SLE is multifactorial and largely unknown, but previous observations have suggested a role for genetic[5,6] hormonal,[7] immunologic,[8,9] and environmental factors.[10] Among these, a dysregulation of the immune system is typical. Furthermore, there is documentation of infectious agents possibly causing the development of the disease via the production of antimicrobial antibodies triggering autoimmunity.[11]

Periodontitis is an infectious and chronic inflammatory disease affecting the tooth supporting tissue consisting of gingiva, periodontal ligament, cementum and alveolar bone (the periodontium). A change in the bacterial composition of the subgingival biofilm may disrupt the homeostasis between the host and bacteria, leading to dysbiosis and tissue destruction in a susceptible host[12] Periodontitis is one of the most prevalent inflammatory diseases worldwide.[13,14] In 2010, severe periodontitis was the sixth most prevalent condition in the world, affecting 11% of the global adult population, thus around 743 million people affected.[13,14] Numerous studies have confirmed that periodontitis not only is a destructor of oral tissue, but also has an association with systemic diseases such as cardiovascular disease,[15,16] osteoporosis,[17–19] and diabetes mellitus (DM) type 2.[17,20] Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by polyarthritis predominantly affecting small joints.[21] A meta-analysis ($n = 153{,}492$) showed an association between periodontitis and RA.[22] Chen et al., in a population-based case-control study, found an association between a history of periodontitis and RA risk and described the association as both dose-and time-dependent.[23]

SLE and RA are both immune-mediated systemic inflammatory diseases having clinical as well as pathogenetic aspects in common.[24–26] The diseases may overlap, sometimes causing a clinical presentation with aspects of both diseases, commonly known as "Rhupus."[27] The etiology of both diseases is largely unknown, although a dysregulation of the immune system possibly triggered by environmental factors is suspected in both conditions. Consequently, as periodontitis seems to play a role in the development of RA, a similar association may be present for SLE.

To date, there is limited research regarding periodontitis in SLE patients. Based on the similarities between RA and SLE as well as a known association between periodontitis and RA, a relation between periodontitis and SLE is likely and could be of importance in the development – and possibly in the treatment of SLE.[28] Consequently, we wished to investigate the prevalence of periodontitis in a large SLE cohort using data from two nationwide registries: the Norwegian Patient registry (NPR) and Norway Control and Payment of Health Reimbursement (KUHR). The use of these large databases offers a unique opportunity to study epidemiological aspects of SLE because of the relative rarity of the disease. We want to explore how the diseases correlate and broaden current knowledge on this topic.

2 | MATERIALS AND METHODS

This is a population-based study using national data from the 10-year period from January 2008 through December 2017 in Norway. Our cohorts were identified based on International Classification of Disease (ICD)-10-codes registered in the Norwegian Patient Registry (NPR). Furthermore, Norwegian procedure codes, also registered in the NPR, were obtained.

2.1 | Ethical considerations

The study was approved by the regional ethics committee (REK) (study reference number 2018/2124/ REK vest). As all data were anonymous and may not be tracked to the individual patients, a dispensation from the claim of informed consent was granted. The project was evaluated by the Norwegian Data Protection Services (NSD) who recommended that a data protection impact assessment—DPIA—was performed to identify and analyze how data privacy might be affected by our project. The handling of data was considered to be in line with the General Data Protection Regulation (GDPR). This article follows STROBE statement.[29]

2.2 | SLE cohort

The study group consisted of patients with SLE defined as individuals 20 to 60 years of age having four or more visits/admissions registered in the NPR with the diagnosis SLE (M32.9) during the 10-year period from 2008-2017. The limit of four or more separate visits or admissions with SLE as a diagnosis was chosen to enhance the probability of a correct diagnosis and reduce the risk of inclusion because of miscoding. Patients having 1 to 3 registrations with M32.9 were excluded. In total, 1,990 SLE patients meeting the inclusion criteria were enrolled. Through NPR we obtained information about the patient's diagnosis, date of birth, sex, presence of DM type 1 and type 2 (E10 and E11), presence of myocardial infarction and date of death, when applicable.

2.3 | Comparative cohort

The control group ($n = 170{,}332$) consisted of patients 20-60 years of age having been treated for assumed non-osteoporotic fractures or having undergone hip- or knee-replacement because of osteoarthritis during the 10-year period from 2008-2017. The fracture patients were identified based on having one or more hospital admissions registered with one of the procedure codes: NFJ (treatment for femoral fracture), NHJ (treatment for ankle fractures) or NBJ (treatment for fracture of the humerus). ICD-10 codes M15 through M19 in combination with one of the following procedure codes: NFB (hip replacement) or NGB (knee

replacement) were used to identify the joint replacement patients. These patient groups were considered suitable controls because of the large number of affected individuals and no known risk factors for periodontitis associated with the diseases. However, diagnostic codes for DM type 1 or 2 or myocardial infarction were allowed in both the study- and control group, and these variables were adjusted for in the analyses. Osteoporosis is a frequent comorbidity in most rheumatic diseases,[30] probably because of the inflammation and the use of corticosteroid treatment. For this reason, we avoided the inclusion of the most osteoporosis-associated fractures (hip, wrist, and spine).

Patients qualifying for inclusion in both the study- and control group, were included in the study-group. Furthermore, we had diagnostic codes for RA and Sjögren's syndrome, and patients otherwise belonging to the control group but having one of these diagnostic codes registered twice or more, were excluded. The age interval 20 to 60 years of age was chosen to reduce the age difference between the SLE cohort and the controls, as the SLE patients are younger.

2.4 | The Norwegian Patient Registry (NPR)

The NPR is a Norwegian central health register established in 1997. NPR's primary task is to assemble information on all subjects having undergone treatment in a Norwegian hospital or outpatient clinic. It includes information regarding diagnosis, treatment, procedure codes and time for admission and discharge. The information is obtained directly from the institutions electronic administrative patient registration system.

2.5 | KUHR

KUHR (Control and Payment of Health Refunds) is a system that handles reimbursement claims from treatment and health institutions to the state. The system is owned by the Norwegian Directorate of Health and it manages settlements for specialists, suppliers and service providers. Reimbursement is provided for systematic treatment of periodontitis and peri-implantitis aimed at achieving infection control. Support is not granted for preventive measures such as routine dental cleaning or for the treatment of gingivitis. For the present study, codes for periodontal treatment and rehabilitation were used, namely code 501 representing systematic treatment of periodontitis and 502 indicating periodontal surgery. To be included in the study, it was required that reimbursement claims for periodontal treatment should have occurred ≥6 times per patient or that periodontal surgery should have been performed during 2008 to 2017. This strict limit was set to avoid including patients where reimbursement claims have been used incorrectly, that is, for patients who do not have periodontitis but are visiting a dentist for general routine recall. The 11-digit Norwegian identification was used to collate data on diagnostic- and procedure codes in the NPR to data on received reimbursement from KUHR.

2.6 | Outcome

The main outcome of our study was the manifestation of periodontitis defined by either at least one registration of code 502 or 6 or more registrations of 501 in the KUHR. These criteria were set to ensure the presence of periodontitis and avoid misclassification because of conscious or unconscious miscoding by the dentist or dental hygienist.

2.7 | Statistics

Qui-square analyses were used to compare categorical variables between patients and controls (e.g., percentage with DM type 2 or percent women, Table 1). We performed logistic regression analyses adjusting for sex, age, the presence of DM type 2, at least one registration of myocardial infarction (MI), and death during the study period. We also performed an identical regression analysis only including female participants and lastly, we performed an analysis including all participants, but in which only periodontal surgery (code 502) was used as the outcome. In the regression analysis (Table 2) age was included as a continuous variable to adjust for age. We also did a regression analysis for each age category (Table 3). The inclusion of death was done because mortality is increased in SLE which could render a falsely reduced risk of periodontitis. Also, because of a major difference in age distribution, sub-analyses within each age category (20-30, 30-40, 40-50, and 50-60 years) were performed. In these analyses, all the above-mentioned factors were initially included, but for the two youngest age groups, DM type 2, MI and death were excluded because of very low numbers in some subgroups. For the 40 to 50 age group, DM type 2 and death were included in the analyses as these were shown to be statistically significant factors in the initial analyses, whereas the same factors were also included for the 50 to 60 age group in addition to the registration of myocardial infarction. In this study, the odds ratio (OR) almost equals the risk because of the high number of included patients and the relative rare outcome.

3 | RESULTS

A total of 1990 patients (90.8% female) were registered with the diagnosis of SLE during the study period and were compared with 170,332 healthy non-SLE controls (51.1% female). Among 1990 SLE patients, 125 (6.3%) were treated for periodontitis compared to 8218 out of 170,332

TABLE 1 Characteristics of Patients and Controls. Crude Numbers and Percentages

	SLE cohort n = 1990	Comparative cohort n = 170332	p-value*
Sex, n (% women)	1807 (90.8)	87012 (51.1)	<0.001
Age in years (n, %)			<0.001
20-30	307 (15.4)	11732 (6.9)	
30-40	501 (25.2)	19488 (11.4)	
40-50	611 (30.7)	48250 (28.3)	
50-60	571 (28.7)	90862 (53.3)	
DM type 2, n (%)	18 (0.9)	4483 (2.6)	<0.001
DM type 1, n (%)	16 (0.8)	1918 (1.1)	0.18
Periodontitis, n (%)	125 (6.3)	8210 (4.8)	0.003
Myocardial infarction, n (%)	22 (1.1)	1412 (0.8)	0.18
Death during study period, n (%)	42 (2.1)	3343 (2.0)	0.62

*p-values derived from unadjusted chi-square analyses.

TABLE 2 Odds Ratio for Periodontitis in SLE Versus Controls, Adjusted for Age, Sex, Diabetes Mellitus Type 2, Myocardial Infarction, and Death During Study Period

	n	Events*	OR†	95% CI†
SLE				
No	170332	8210	1	
Yes	1990	125	1.78	1.47 – 2.14
Age ‡			1	
			1.06	1.05 – 1.06
DM type 2§				
No	167821	8003	1	
Yes	4501	332	1.53	1.37 – 1.72
Sex				
Men	83503	3174	1	
Women	88819	5161	1.40	1.34 – 1.47
MI‖				
No	170888	8213	1	
Yes	1434	122	1.76	1.46 – 2.13
Death				
No	168937	8271	1	
Yes	3385	64	0.31	0.24 – 0.40

*Events are occurrence of periodontitis.
†OR is odds ratio, 95% CI is 95% confidence interval. Estimates derived from logistic regression analysis.
‡Age was included as a continuous variable and the OR refers to each increasing year of age.
§DM type 2 is diabetes mellitus type 2.
‖MI is myocardial infarction.

(4.8%) controls ($P = 0.003$, Table 1). There was a difference between the patient and control groups regarding age and DM type 2 distribution with more SLE-patients being in the younger age groups and fewer SLE-patients having DM type 2 (Table 1).

The mean number of periodontal treatments registered as code 501 was 1.01 for the SLE group and 0.77 for the controls. In the adjusted analysis, the odds for periodontitis was significantly higher in SLE patients compared to controls (OR 1.78, 95% CI 1.47-2.14, Table 2). A total of 33% of the SLE patients who had received periodontal treatment had undergone periodontal surgery (code 502). In the separate analysis using only code 502 (periodontal surgery) as outcome the OR for periodontitis was 1.57 (95% CI 1.14-2.15), for SLE patients versus controls. Also, the odds for periodontitis in SLE patients was comparable to that in patients having undergone MI or having DM type 2 (Table 2). Furthermore, increasing age was associated with increased risk of periodontitis (Table 2).

In the analysis including only females, the OR for periodontitis was 1.72 ($P < 0.001$, 95% CI 1.41-2.09) for SLE women versus controls (women).

Because of the major difference in age distribution, separate analyses were performed for each age stratum. In three categories, 20 to 30, 30 to 40 and 50 to 60 years, SLE was associated with significantly increased risk of periodontitis (Table 3). In these three age strata, SLE was the strongest risk factor and in the youngest age group, the odds for periodontitis were 3 times that of the non-SLE group. The impact of sex was relatively equal for all groups (OR around 1.4 for woman versus men), although not significant for the youngest age group, possibly because of the lower number of patients in this group.

4 | DISCUSSION

This large nationwide study shows an almost doubled risk of periodontitis in SLE patients compared to the general population. In general, studies reporting on periodontitis

TABLE 3 Odds Ratio for Periodontitis in SLE Versus Controls in Four Age Categories

Covariates	n	Events*	OR†	95% CI†
Age 20-30‖	12939	55		
SLE				
No	11732	50	1	
Yes	307	5	3.24	1.23 – 8.52
Sex				
Men	7679	29	1	
Women	4360	26	1.40	0.81 – 2.44
Age 30-40‖	19989	346		
SLE			1	
No	19488	329		
Yes	501	17	1.73	1.04 – 2.86
Sex				
Men	11719	171	1	
Women	8270	175	1.41	1.13 – 1.75
Age 40-50‖	48861	1852		
SLE				
No	48250	1821	1	
Yes	611	31	1.19	0.83 – 1.72
Sex				
Men	24691	778		
Women	24170	1074	1.43	1.30 – 1.57
DM type 2‡				
No	47847	1798	1	
Yes	1014	54	1.49	1.13 – 1.97
Death				
No	48184	1843	1	
Yes	677	9	0.34	0.18 – 0.66
Age 50-60‖	91433	6082		
SLE				
No	90862	6010	1	
Yes	571	72	1.88	1.47 – 2.42
Sex				
Men	39414	2196	1	
Women	52019	3886	1.37	1.30 – 1.45
DM type 2‡				
No	88129	5811	1	
Yes	3304	271	1.30	1.14 – 1.48
Death				
No	88987	6027	1	
Yes	2446	55	0.32	0.25 – 0.42
MI§				
No	90314	5975	1	
Yes	1119	107	1.65	1.35 – 2.02

*Events are occurrence of periodontitis.
†OR is odds ratio, 95% CI is 95% confidence interval. Estimates derived from logistic regression analysis.
‡DM type 2 is diabetes mellitus type 2.
§MI is myocardial infarction.
‖For the two youngest age groups no or very few patients had DM type 2, MI, or died, leaving subgroups with 0 events. For this reason, these variables were not included in the analyses. For the two older age groups, DM type 2 and death were included and MI for the 50-60 group.

prevalence in SLE compared to a control population are scarce, as illustrated by the review by Rutter-Locher et al. from 2017 in which eight studies were included.[31] In that study however, the risk estimate for periodontitis in SLE patients was very similar to that found in our study (RR 1.75 and OR 1.78, respectively).

One cross-sectional study including 25 SLE patients from Saudi-Arabia reported that periodontal health was not different between SLE and healthy controls,[32] whereas another study including 27 SLE patients found that periodontal parameters were less severe in SLE patients.[33] Altogether the majority of previous publications agrees with our finding of an increased periodontitis rate in SLE.[31]

A nationwide case-control study from Taiwan found an association between history of periodontitis and newly diagnosed SLE.[34] In their study, the risk of SLE was estimated in patients having undergone periodontitis, whereas we focused on the risk of periodontitis in SLE-patients, which could explain their finding of a weaker estimate of association. We also found a higher risk estimate for SLE than for DM type 2 which is a known risk factor for periodontitis.[20]

In our study, the association between SLE and PD was seen in the whole SLE group, but the risk of periodontitis was particularly increased in the youngest age group, in whom periodontitis is otherwise a rare condition. The association was seen in all age categories except for participants aged 40 to 50 years. Calderaro et al., in a study from 2016, found a tendency towards periodontitis occurring earlier in SLE subjects, which corresponds to our findings.[35] In older individuals, periodontitis is generally frequent, whereas it may be particularly important to address this in younger patients in whom periodontitis is normally a less often condition.[13]

There could be several reasons for the observed association between SLE and PD. As there seems to be an association between periodontitis and some autoimmune diseases, such as RA,[17,23], genetic, immunological, and environmental factors could all play a part. SLE and periodontitis share some pathophysiologic characteristics. In addition to an important role of B-lymphocytes in the pathogenesis[36,37] the two conditions share similar inflammatory profiles.[38,39] Kobayashi et al. found higher expression of Fcγ receptor polymorphisms in patients with SLE and periodontitis versus patients with SLE without periodontitis.[40] Periodontal tissue damage derives from an excessive and unregulated production of different inflammatory mediators in response to the presence of infectious agents in the dental biofilm.[41,42] Infectious processes are associated with SLE onset and exacerbation as well and the pathogens most frequently described are viruses.[43] Thus, common risk factors and pathogenetic factors for periodontitis and SLE could partly explain the association.

There are few publications addressing the impact of corticosteroid treatment on periodontal disease, but one recent review concluded that some studies indicate an adverse effect of corticosteroids.[44] Furthermore, Fernandes et al. found a positive association between the cumulative dose of corticosteroids and increase in plaque and gingival bleeding rates in patients with juvenile SLE ($P = 0.01$), whereas no association with the use of antimalarials or immunosuppressive agents was established.[45] Because corticosteroid treatment is part of the treatment regime for a majority of SLE patients, this could also contribute to the increased rate of periodontitis seen in the SLE-patients of our study.

The prevalence and extent of periodontitis increases with age, and it is often reported that periodontal diseases and periodontal tissue loss are more prevalent in males than in females.[46,47] We found higher odds of periodontitis in females. This could be related to the study design in which periodontitis was defined by a procedure code being used a certain number of times. Thus, if women seek help more often than men, this could cause this effect. As this is a population-based study, we do not have information on the severity of the periodontitis, which could be worse in men.

A major strength of this study is the large study- and control populations encompassing the Norwegian population with the chosen diagnoses and procedures during a 10-year period. We are not aware of any studies addressing this subject with a comparably sized study population. The detected almost doubled rate of periodontitis in the SLE patients is thus reliable. The large control group from the same time period was important to control for time-dependent factors (e.g., the coding of periodontitis) as both patients and controls will most likely have been equally affected by potential changes.

To be included in the study, it was required that reimbursement claims for periodontal treatment should have occurred ≥6 times per patient or that periodontal surgery should have been performed, which increases the robustness of our study. This strict limit was set to avoid including patients where reimbursement claims have been used incorrectly, i.e., for patients who do not have periodontitis but are visiting a dentist for general routine recall.

The design of our study makes us unable to describe the *nature* of the association between SLE and periodontitis. Which is the cause, and which is the result may not be answered and the association could also be because of common etiological factors. However, as an association between RA and periodontitis is well established and periodontitis may be involved in the pathogenesis of RA, a similar association between SLE and periodontitis is plausible and should be further explored.

There is a significantly higher risk for periodontal disease in smokers compared to non-smokers, and the increased risk is proportional to the duration and rate of smoking. [47–50] Smokers exhibit deeper pockets, more extensive and severe attachment loss, and a higher rate of tooth loss.[51] Clinical treatment outcomes of non-surgical and surgical therapies as well as the long-term success of implant placement is also affected by smoking.[52,53] Of note, smoking has also been associated with increased risk of SLE.[54] This was first shown by Costenbader et al.[55] in a meta-analysis of seven case-control and two cohort studies which found a significant risk for the development of SLE among current smokers compared to non-smokers (OR 1.50, 95% CI 1.09–2.08), but not past smokers (OR 0.98, 95% CI 0.75–1.27). Later, a meta-analysis by Jiang et al. 2015 found that OR for SLE risk was 1.56 (95% CI = 1.26–1.95) among current smokers compared with nonsmokers.[56] For ex-smokers versus nonsmokers, the pooled OR for SLE risk was 1.23 (95% CI = 0.93–1.63). For register-based studies one known limitation is the possible impact of factors not registered. Unfortunately, neither the NPR register nor KUHR contain information of smoking, so smoking habits, as well as other unknown confounding factors could not be adjusted for in the present study.

Obesity is another factor which has been related to tooth loss and periodontitis.[57,58] A systematic review with meta-analysis reported that obese individuals had 81% higher odds of having periodontitis than normal weight individuals,[58] however, results are conflicting and periodontitis was not significantly associated with obesity status in a recent epidemiological study from the US.[47] The Norwegian Patient Registry does not contain information on obesity, and a possible influence of obesity on our results could not be answered.

Another weakness of the study is that diagnoses were based on diagnostic codes and were not verified by a journal review. The requirement of at least four registered codes for SLE will have minimized the risk of misclassification but will also have caused the exclusion of some SLE patients. Altogether, our study cohort may lack a few patients, but we have good reason to think it representative of the SLE-cohort. Furthermore, the outcome was defined by procedure codes and we may have under- or overestimated the frequency of periodontitis-treatment. However, a possible under- or overestimation would, presumably, be the same in the SLE patients as well as the controls, and the detected difference should still be true. Finally, the control cohort was also selected based on disease and procedure codes. Although we have little reason to suspect that patients with non-osteoporotic fractures or osteoarthritis of the hip or knee have an altered periodontitis risk, some may have had comorbidities associated with

periodontitis risk, aside from DM type 2 and coronary heart disease, which were adjusted for. The large number of controls would serve to correct for uncommon comorbidities which could otherwise have influenced the results. Also, selecting only patients 20-60 years of age and performing age-stratified subanalyses, were done to adjust for the age difference between the patients and controls.

5 | CONCLUSION

In summary, the results of this large nationwide study showed an almost doubled risk of periodontitis in SLE-patients compared to a control population. The difference was most evident in the young SLE-patients. We believe the findings of our study warrants an increased focus on dental health in SLE-patients.

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CONFLICT OF INTEREST

The authors state explicitly that there are no conflicts of interest in connection with this article, and the authors have no commercial relationships to declare.

AUTHOR CONTRIBUTIONS

Anne Isine Bolstad, Stein Atle Lie and Bjørg-Tilde Svanes Fevang: conception and design; acquisition, analysis and interpretation of data; drafting article. Pria Sehjpal: design, drafting article. Additionally, all of the authors meet all of the following criteria established by the International Committee of Medical Journal Editors: (1) drafting the article or revising it critically for important intellectual content; (2) final approval of the version to be published; and (3) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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