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ORIGINAL ARTICLE

Periodontitis in patients with primary Sjögren's syndrome: A nation-wide register study

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Abstract

The aim of this study was to compare the occurrence of periodontitis in patients with primary Sjögren's syndrome (pSS) and a non-Sjögren's patient group during a 7-year period from 2011 through 2017. In this population-based study, the patients were identified based on the International Classification of Diseases-10 (ICD-10) codes registered in the Norwegian Patient Registry (NPR), which contains information on diagnosis and time of admission for all hospitalized patients in Norway. The pSS group comprised patients with ≥4 registrations with ICD-10 code M35.0 (Sjögren's syndrome) as the main diagnosis. The dependent variable was periodontitis, defined by procedure codes registered in the Norwegian Control and Payment of Health Reimbursement (KUHR). Logistic regression analyses estimated the odds ratio for periodontitis in pSS patients relative to non-pSS patients, adjusted for relevant covariates. Lastly, regression analyses were performed separately for each of the 6 age categories. In total, 760 (7.5%) patients in the pSS group and 22,178 (7.1%) in the non-pSS group had periodontitis. When adjusting for covariates, the presence of pSS had no association with periodontitis (OR = 1.06, 95% CI: 0.98–1.14).

KEYWORDS

autoimmune diseases, epidemiology, inflammation, periodontal diseases, primary Sjögren's syndrome, registries

INTRODUCTION

Sjögren's syndrome is a systemic autoimmune disorder characterized by focal lymphocytic infiltration of the exocrine glands, causing dry eyes and dry mouth [1]. Other hallmarks of the disease are elevated proinflammatory cytokines and circulating autoantibodies [2]. Patients often experience significant fatigue and a decrease in quality of life [3–5]. Patients with Sjögren's syndrome also have greater dental caries experience [6], more tooth extractions [7], and higher dental expenses than healthy controls [8, 9].

The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) in 2016 made a set of classification criteria for the diagnosis of primary Sjögren's syndrome (pSS). The main criterion is a clinical presentation of dry eyes and/or dry mouth. Other aspects that support the diagnosis are positive serum anti-SSA (anti-Ro) antibodies, focal lymphocytic sialadenitis

in labial salivary gland biopsy with a focus score of ≥1 foci/4 mm^2, a Schirmer test result of ≤5 mm/5 min, unstimulated whole saliva flow rate ≤0.1 mL/min, and an Ocular Staining Score ≥5 in at least one eye. The final classification criteria are based on the weighted sum of these 5 items, thus ensuring that objective measures are being met to achieve the diagnosis [10].

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth supporting tissues, which consist of gingiva, periodontal ligament, cementum, and alveolar bone [11, 12]. The condition is relatively common [13], affecting around 11% of the world's population, and is a major cause of tooth loss worldwide [14]. In a Norwegian population-based study, the most severe forms of periodontitis (stage III and stage IV combined) were observed in 17.6% of the population [15].

Several studies have confirmed associations between periodontitis and systemic diseases, among them diabetes mellitus (DM) type 2 [16, 17] and cardiovascular disease [18, 19]. The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [12], which described the diagnostic criteria for periodontitis currently being enforced, defined DM and smoking as risk factors for poorer outcomes. An association between the inflammatory autoimmune joint disease rheumatoid arthritis (RA) and periodontitis has also been shown [20, 21]. They are both chronic inflammatory diseases and have similarities in their biological mechanisms, histopathology, and socio-demographic pattern [22]. Bolstad et al. [23] showed a similar association between systemic lupus erythematosus (SLE) and periodontitis. The clinical presentations of RA and Sjögrent's syndrome show common features. Patients with RA may experience reduced tear production and dry eyes [24], while joint pain is a common symptom in patients with Sjögren's [8]. With these similarities in mind, it is of interest to investigate whether people with pSS have a higher frequency of periodontitis than the normal population. A recent systematic review showed that Sjögren's syndrome was not a risk factor for periodontitis [25]. In that review, however, patients who had undergone periodontal treatment were excluded from all studies; therefore, it is not known whether more patients were excluded from the Sjögren's syndrome groups than from the control groups, and whether this may have influenced the findings. A meta-analysis by Wu et al. [26] concluded that there is a need for a large-scale study to determine whether an association exists. Since patients with Sjögren's syndrome already have a high risk of dental caries and associated tooth loss, addressing periodontal health is of particular interest for this patient group [27].

The objective of this study was to investigate whether periodontitis is more frequent in patients with pSS than in a non-Sjögren's patient group.

MATERIAL AND METHODS

This was a nation-wide population-based study where the patient groups were identified using International Classification of Disease (ICD)−10-codes registered in the Norwegian Patient Registry (NPR) during the period January 2011 to December 2017. Patients were included based on diagnoses in the NPR. No matching was performed; all patients with a diagnosis of interest were included.

This study was approved by the regional ethics committee (REK) (reference number 2018/2124/REK Vest) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013 [28]. A dispensation from the requirement of informed consent was granted, since all the data were anonymous and, thus, not possible to link to individual patients. All data were handled according to the rules laid down in the General Data Protection Regulation (GDPR). This article follows the Strengthening the Reporting of Observational Studies (STROBE) Statement checklist [29].

Norwegian Patient Registry (NPR)

The NPR is a Norwegian central health registry established in 1997. The NPR collects data on all patients that have undergone treatment in Norwegian specialist care, including admissions and outpatient visits. Data are delivered automatically from the hospitals' patient administrative systems, rendering a close to 100% completeness. The registry includes information on diagnosis, procedure codes, and time of admission and discharge.

Control and Payment of Health Reimbursements Database (KUHR)

The KUHR is a public institution owned by the Norwegian Directorate of Health that handles reimbursement claims from clinics and health institutions. Reimbursement is granted for systematic treatment of periodontitis and peri-implantitis. However, support is not granted for preventive measures, such as treatment of gingivitis or routine cleaning of the teeth. For this study, we used code 501 (representing systematic treatment for periodontitis) and code 502 (used for periodontal surgery). The patientt's personal Norwegian identification number was used to link the procedure and diagnostic codes in the NPR to the reimbursement codes in the KUHR.

The outcome (dependent variable) of the study was periodontitis, defined as at least six registrations of periodontal treatment (code 501) or one registration of periodontal surgery (code 502) in the KUHR during the study period

(2011−2017). This definition was set to ensure that actual cases of periodontitis were identified, since one (or a few) registration(s) may have been used incorrectly.

Sjögren's syndrome patient group

The Sjögren's syndrome group (n = 10,086) consisted of all patients aged 20−80 years who had four or more hospital admissions/out-patient visits registered with M35.0 as the main diagnosis in the NPR during the study period. The case definition based on four or more separate visits was used to ensure a correct diagnosis and to decrease the risk of miscoding. Patients having two or more diagnostic codes of RA or SLE were excluded because these diagnoses are closely related to Sjögren's syndrome and were thus not expected to be evenly distributed across patients and the comparison group. Having one to three registered M35.0 coding was also an exclusion criterion. Demanding at least four M35.0 codes as main diagnostic codes, along with the exclusion of patients with more than one RA code, ensured that the Sjögren's syndrome study group predominantly consisted of pSS. Through NPR, we obtained information about the patient's diagnosis, gender, date of birth, presence of DM type 1 (DM1) and type 2 (DM2) (E10 and E11, respectively), history of myocardial infarction (MI) (I21), and date of death (when appropriate). To be recorded as having DM1 or DM2, at least four registrations were required with DM1 or DM2 as the main diagnosis in the NPR.

Comparison group

The comparison group (n = 310,573) consisted of patients 20−80 years of age, who had been treated for non-osteoporotic fractures or had undergone knee or hip replacement due to osteoarthritis during the study period (2011−2017). The fracture patients were identified based on their having one or more hospital admissions registered with one of the following procedure codes: NFJ (treatment for femoral fracture), NHJ (treatment for ankle fractures), or NBJ (treatment for fracture of the humerus). The joint replacement patients were included if they were registered with ICD-10 codes M15 through M19 in combination with one of the following procedure codes: NFB (hip replacement) or NGB (knee replacement).

These patients were considered suitable as a comparison group due to the large number of affected individuals and due to their conditions posing no known risk for periodontitis. We avoided including osteoporosis-associated fractures (hip, wrist, and spine fractures) because osteoporosis is a common comorbidity in several rheumatic diseases. Patients in the comparison group who were registered with two or more diagnostic codes for RA or SLE were excluded because of the overlap in disease manifestations with Sjögren's syndrome and the known association of these conditions with periodontitis [21, 23]. Age and gender differences between patients and the comparison group were adjusted for in the analyses.

Statistical analyses

Cross-tabulations and t-tests were used to analyze categorical and continuous variables, respectively, between the Sjögren's syndrome patients and the comparison group. Logistic regression analysis with periodontitis as the dependent variable and Sjögren's syndrome, age, sex, DM1, DM2, MI, and death as the independent variables was used to calculate the odds ratio (OR) and 95% CI for periodontitis. Because periodontitis is more common with age [30], we divided the samples into six different age groups and repeated the analyses for each age group. MI and death were adjusted for in the analyses, but the data were not presented in the tables to improve the readability.

RESULTS

Patient characteristics were generally similar for patients and the comparison group, except for there being more women in the Sjögren's syndrome group (Table 1). During the study period, 760 (7.5%) patients in the Sjögren's syndrome group and 22,178 (7.1%) in the comparison group ($p = 0.131$) were treated for periodontitis.

When adjusting for age, sex, DM1 and DM2, MI, and death, the presence of pSS was not statistically significantly associated with periodontitis occurrence (OR = 1.06, 95% CI: 0.98−1.14) (Table 2). Furthermore, higher age was associated with a higher risk of periodontitis (OR = 1.03, 95% CI: 1.02−1.03), as well as DM1 (OR = 1.32, 95% CI: 1.17−1.50) and DM2 (OR = 1.19, 95% CI: 1.10−1.27).

There were 75,095 patients within the 50–59-year-old subgroup, and 2,386 (3.2%) of these had pSS. Among the latter, 231 (9.7%) had periodontitis, while 5,463 (7.5%) had periodontitis within the non-Sjögren's syndrome group in the same age stratum. In the 50−59 years age group, the presence of pSS was statistically significantly positively associated with periodontitis (OR = 1.22, 95% CI: 1.06−1.40). There was no such association observed in any of the other age groups (Table 3).

DISCUSSION

In this study, we combined data from two national registries to investigate the association between pSS and periodontitis.

TABLE 1 Characteristics of study participants.

Variables	Sjögren's syndrome group (n = 10,086) n (%)	Comparison group (n = 310,573) n (%)	p-value*
Sex			
Female	8090 (80.2)	176,122 (56.7)	**<0.001**
Median age (IQR)	59 (20.0)	62 (18.0)	**<0.001**
Age in years			
20–29	525 (5.2)	9125 (2.9)	–
30–39	817 (8.1)	14,517 (4.7)	–
40–49	1439 (14.3)	39,217 (12.6)	–
50–59	2386 (23.7)	72,709 (23.4)	–
60–69	2852 (28.3)	94,506 (30.4)	–
70–80	2067 (20.5)	80,499 (25.9)	–
Periodontitis	760 (7.5)	22,178 (7.1)	0.131
DM1	105 (1.0)	3139 (1.0)	0.764
DM2	292 (2.9)	9818 (3.3)	0.132
MI	327 (3.2)	10,382 (3.3)	0.579
Death during study period	296 (2.9)	16,464 (5.3)	**<0.001**

Abbreviations: DM1, Diabetes mellitus type 1; DM2, Diabetes mellitus type 2; IQR, interquartile range; MI, Myocardial infarction.

*p-values derived from chi-square analyses for categorical variables and t-test for continuous variables. Significant p-values are highlighted in bold.

TABLE 2 Logistic regression model for periodontitis.

Variables	OR	95% CI
Primary Sjögren's syndrome	1.06	0.98–1.14
Age	1.03	1.02–1.03
Female	1.25	1.21–1.28
DM1	1.32	1.17–1.50
DM2	1.19	1.10–1.27
MI	1.03	0.96–1.11
Death during study period	0.33	0.30–0.35

Note: Age, Age was included as a continuous variable and the OR refers to each increasing year of age.

Abbreviations: CI, Confidence interval; DM1, Diabetes mellitus type 1; DM2, Diabetes mellitus type 2; MI, Myocardial infarction; OR, odds ratio.

TABLE 3 Logistic regression model for periodontitis in 6 age strata.

	OR	95% CI
Age 20–29		
Primary Sjögren's syndrome	1.96	0.65–5.88
Female	1.15	0.58–2.28
Age 30–39		
Primary Sjögren's syndrome	1.04	0.62–1.75
Female	1.38	1.07–1.77
Age 40–49		
Primary Sjögren's syndrome	1.25	0.98–1.59
Female	1.35	1.22–1.50
DM1	2.15	1.54–3.00
DM2	1.60	1.19–2.16
Age 50–59		
Primary Sjögren's syndrome	1.22	1.06–1.40
Female	1.41	1.34–1.50
DM1	1.26	0.99–1.61
DM2	1.45	1.26–1.67
Age 60–69		
Primary Sjögren's syndrome	0.98	0.87–1.11
Female	1.24	1.19–1.30
DM1	1.13	0.92–1.39
DM2	1.05	0.94–1.17
Age 70–80		
Primary Sjögren's syndrome	0.97	0.82–1.15
Female	1.07	1.02–1.14
DM1	1.28	0.92–1.62
DM2	0.96	0.83–1.11

Note: For the two youngest age groups, none or very few patients had DM1, DM2, myocardial infarction, or died. For this reason, these variables were not included in the analyses. In addition to the shown factors, myocardial infarction and death were adjusted for in the four oldest age groups.

Abbreviations: CI, Confidence interval; DM1, Diabetes mellitus type 1; DM2, Diabetes mellitus type 2; OR, Odds ratio.

We found no statistically significant association. Our findings agree with those of Maarse et al. [25] and de Goés Soares et al. [31], who reported similar findings, although in smaller studies with less statistical power. Patients aged 50–59 years had a somewhat higher occurrence of periodontitis and presented a statistically significant association between pSS and periodontitis, while no association was seen in the other age groups. One reason for this could be that older age is strongly associated with periodontitis, and a higher risk due to pSS would have very little impact on the total risk in the oldest age groups. Consequently, if pSS is associated with periodontitis at all, the association is weak and probably of limited clinical relevance. Other factors, such as smoking, DM, and obesity, will be far more important.

This study had some limitations. Many factors possibly influencing periodontitis were not known to us due to the nature of this registry study. To adjust for this, we used a comparison group consisting of patients with admissions for non-osteoporotic fractures or joint replacement procedures due to osteoarthritis. Not having compared with the general population might also have influenced our findings, since a possibly higher prevalence of periodontitis in our comparison group could have negated a possible higher frequency in the Sjögren's syndrome group. There is, however, little evidence to support this, and in two previously published studies

addressing RA and SLE, a similar comparison group was used and a higher prevalence of periodontitis was found for both RA and SLE [21, 23]. Furthermore, there is a known association between smoking and the development of periodontitis, and the higher risk is proportional to the duration and frequency of smoking [11, 32–34]. Obesity is also associated with a higher risk of periodontitis, although the mechanisms are unclear [35]. The NPR does not include information on smoking, obesity, or other lifestyle factors, and so we were not able to adjust for these. However, no connection between Sjögren's syndrome and obesity is known, and neither is there a known higher prevalence of smokers among patients with Sjögren's syndrome. Using diagnostic codes to define the patient groups may have caused some erroneous inclusions, but the strict case definition of at least four registrations with Sjögren's syndrome as the main diagnosis was likely to have greatly reduced the risk of miscoding. Similarly, periodontitis was defined as present when at least 6 registrations of routine treatment of periodontitis, or one coding of periodontal surgery, was found. This likely minimized the risk of erroneous registration of periodontitis, although we would have excluded periodontitis in patients having had fewer than 6 treatment codes. This would apply to both groups, however. A major strength of this study was the large patient population (including the entire Norwegian population) with the given diagnoses and procedures within a 7-year period. To our knowledge, there are no other studies on the topic with a similarly large population size.

Previous studies have shown that patients with RA or SLE are more prone to developing periodontitis [21, 23, 36, 37]. This association is complex and not yet fully understood, but the similarities in immunological profiles and cytokine levels seem to play an important role [36, 38]. The lower level of inflammation in Sjögren's syndrome than in diseases such as RA and SLE could account for the higher prevalence of periodontitis in these diseases than in Sjögren's syndrome patients.

We found that higher age was associated with the presence of periodontitis. This is consistent with findings from previous studies in Norway [13, 15, 30, 39]. Previous findings have, however, shown that men have a higher prevalence of periodontitis than women [13, 40], while our study showed the opposite. This finding could be connected to the study design, as the manifestation of periodontitis was defined by a certain number of procedure codes registered in connection with dental treatment. Women would, accordingly, be registered more often with periodontitis if they were to seek help more often than men, which has been shown to be the case in several studies [41, 42]. Even so, we believe this would pertain similarly to patients in the Sjögren group and the comparison group. The study also showed that DM2 was associated with periodontitis, which is in line with previous findings [17].

In this study, based on a large national data set, no higher occurrence of periodontitis was found in primary Sjögren's patients than in the comparison group. Using the same data material, including the same comparison group, we previously found a higher risk of periodontitis in patients with RA and SLE [21, 23]. Not detecting a difference between the pSS patients and the comparison group in this study strongly suggests that no relevant association is present. Consequently, patients with pSS do not need a different intensity of periodontal follow-up from that already indicated by the disease itself. In conclusion, the occurrence of periodontitis was not higher in pSS patients than in the comparison group in this large nationwide study.

AUTHOR CONTRIBUTIONS

Conceptualization: Odd-Olav Aga, Bjørg-Tilde Svanes Fevang, Anne Isine Bolstad, Stein Atle Lie; **Methodology**: Odd-Olav Aga, Bjørg-Tilde Svanes Fevang, Anne Isine Bolstad, Stein Atle Lie; **Formal analysis**: Odd-Olav Aga, Bjørg-Tilde Svanes Fevang, Anne Isine Bolstad, Stein Atle Lie; **Writing—Original draft**: Odd-Olav Aga; **Writing—Review and editing**: Bjørg-Tilde Svanes Fevang, Anne Isine Bolstad, Stein Atle Lie.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest related to this study and have no commercial relationship to declare.

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