Oral lesions in Sjögren’s syndrome: A systematic review

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Abstract
Background: Sjögren’s syndrome (SS) is an autoimmune disease related to two common symptoms: dry mouth and eyes. Although, xerostomia and hyposialia have been frequently reported in these patients, not many studies have evaluated other oral manifestations. The aim of this systematic review was to investigate prevalence rates of oral lesions (OL) in SS patients and to compare it to a control group (CG), when available.

Material and Methods: An exhaustive search of the published literature of the Pubmed, Scopus, Web of Science and the Cochrane Library databases was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) for relevant studies that met our eligibility criteria (up to September 1st 2017).

Results: Seventeen cross-sectional studies and one cohort study were finally included. The results showed that SS patients presented more OL compared to non-SS patients. The most frequent types of OL registered in primary and secondary SS were angular cheilitis, atrophic glossitis, recurrent oral ulcerations and grooves or fissurations of the tongue, also when compared to a CG.

Conclusions: OL are common and more frequent in SS patients when compared to a CG. This may be a consequence of low levels of saliva. More studies where these OL and all the possible cofounding factors are taken into account are needed.

Key words: Sjögren’s syndrome, oral lesions, oral diseases, oral manifestations, oral disorders, systematic review.
Introduction
Sjögren’s syndrome (SS) is one of the most frequent autoimmune rheumatic diseases. It affects 0.5-1% of the population, occurring more middle-aged women than men, with a ratio of 9:1 (1). Although it can appear at any age, it usually arises between the fourth and sixth decade of life. SS is a systemic exocrinopathy of unknown etiology, which mainly affects the lacrimal and salivary glands giving rise to dry eyes and hyposalivation. It may manifest as primary SS (pSS), which occurs as an isolated disease, or as secondary SS (sSS) when it appears simultaneously with other autoimmune disease (1-3). There have been many classification criteria suggested for pSS (4,5). Nowadays, the most widely used is the one proposed by the American-European Consensus Group in 2002 (6). Other diagnosis criteria also accepted are the ones proposed by the American College of Rheumatology and the Sjögren’s International Collaborative Clinical Alliance for pSS (7).
Saliva has an important role in preserving oral health. Therefore, hyposalivation (or hyposialia) frequently increases the risk for different oral problems such as tooth decay, periodontal disease or fungal infections (8-13). Tongue alterations and non-specific ulceration have also been reported (9,14). The association between SS and oral lesions of autoimmune etiology as lichen planus, recurrent aphthous stomatitis, pemphigus vulgaris and mucous membrane pemphigoid remains unclear (15).
This is the first systematic review that unifies all the oral lesions (OL) -non-xerostomia and/or hyposalivation- shown in the SS patients. The objective of the present study was to evaluate which OL are the most frequent in SS patients and compare them with a control group (CG). Knowing this, future dental protocols could be carried out, with the aim of improving SS patient’s oral health and quality of life.

Material and Methods
This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement (16).
-Focused question
Based on the PRISMA guidelines, 2 focused PICO (population, intervention, comparison, and outcome) questions were constructed: 1) Which are the most frequent OL (non-xerostomia and/or hyposalivation) in SS patients? 2) Do SS patients have a higher prevalence of these OL when compared to a CG?
-Search Strategy
A comprehensive search of the scientific literature was conducted without date restriction until September 1st 2017, in the following databases: PubMed/MEDLINE, Scopus, Web of Science and The Cochrane Library by two independent researchers (JS, JGS). The search strategy used was: (“Sjögren syndrome” OR “Sjögren’s syndrome”) AND (“oral manifestations” OR “oral lesions” OR “mucosal lesions” OR “oral diseases” OR “oral pathology” OR “oral mucosal alterations” OR “oral repercussions”) according to each database (Fig. 1). Furthermore, an additional manual search was performed to find potential eligible studies as reference lists of review articles and relevant studies.
-Study selection
•Inclusion criteria. Full-text articles were included regardless of time period of study and year of publication.
Types of studies. The studies included had to be (a) original articles published in scientific journals, (b) cross-sectional or cohort studies, (c) comparative studies (SS group and CG), if available, (d) only in humans, and (e) written in English language.
Types of population. Individuals with SS that could have pSS and sSS (no restriction for SS diagnosis classification criteria was applied). CG population had to be healthy patients.
Outcomes. We considered oral alterations, oral manifestations and oral repercussions as OL. Neither xerostomia nor hyposalivation were included as OL. In addition, we did not include dental lesions or periodontal disease. We considered oral candida lesions when clinical changes, such as angular cheilitis, atrophic glossitis, erythematous candidiasis, pseudomembranous candidiasis, or median rhomboid glossitis were described. We did not consider only positive cultures as OL. The studies must evaluate the presence of oral mucosal lesions and specify the number and/or percentage in the SS group, and the CG, if available.
•Exclusion criteria. (a) Those articles published in a language other than English, and (b) review articles, experimental studies, case reports, commentaries and letters to the Editor.
-Data collection and extraction
Two independent researchers (JS and JGS) compared search results to ensure completeness and then duplicates were removed. Both reviewers individually screened all full title and abstract of the identified articles. Differences in eligible studies were resolved by discussion with a third reviewer (RMLP). Relevant full-text articles were obtained, and checked for eligibility using the following standard abstraction forms: first authors, journal, country in which was conducted, title of the paper, type of study, recruitment of patients, sample characteristics (population, age, and gender of SS patients and CG, when available), type of SS, diagnosis criteria for SS, and oral mucosal diseases diagnosis criteria (Table 1, 1 continue). In Table 2, 2 continue, we reported the prevalence of the different OL in SS patients and CG and, the statistical signification if there was CG, and it was available.
Fig. 1. Flow diagram of the literature search, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Quality Assessment
The Joanna Briggs Institute Prevalence Critical Appraisal Tool (JBI) for Studies Reporting Prevalence Data (17) was used to evaluate the methodological quality of the selected studies (Table 3). A study was considered to have a low quality assessment if a 0-5 criteria was met, and high quality assessment if studies met 5-10 criteria. Two reviewers (JS and JGS) conducted independently a critical appraisal, comparing and discussing afterwards their results. If the two reviewers disagreed on the final critical appraisal, a third reviewer (RMLP) was required.

Categorization of Studies
In order to clarify the results, we categorized the studies in different groups: 1) studies which determine the prevalence of any type of OL, 2) studies which only determine the prevalence of Candida albicans lesions and 3) studies which determine the prevalence of OL of autoimmune aetiology.

Data items and synthesis of results
The prevalence of oral mucosal lesions from the included studies was presented as a percentage. This percentages and their statistical significance, when available, shown along with the number of SS and CG (when available), were recorded in Table 2, 2 continue. A meta-analysis was not possible to carry out due to the differences between the selected papers: different types of SS, different SS diagnosis criteria, lack of agreement in OL diagnosis, and absence of healthy CG in some of the studies.

Results

Study selection
The search strategy yielded 467 results, of which 310 remained after removing duplicates. We screened all the titles, excluding those written in any language other than English, and those that were out of scope of review, obtaining a total of 56 eligible publications. Then, two independent researchers (JS and JGS) reviewed all the titles and abstracts, and excluded those that were reviews, case reports or did not specify oral disorders. Due to the study populations in the papers carried out by Soto-Rojas (14,18) were exactly the same (with the same result data) we considered both publications as only one article in order to unify the oral manifestations. The same resolution was taken for those carried out by Rhodus (19,20). Thirty-six studies, which did not
Table 1. Study characteristics.

| Author et al; Year | Journal | Type of study | Patients recruited at | Sample (Denture wearers) | Mean age (years) | Gender (F %) | Type of SS Classification criteria | Oral mucosal evaluation |
|--------------------|---------|---------------|-----------------------|--------------------------|-----------------|-------------|------------------------------------|------------------------|
| Federsen et al; 1999 | Oral Diseases | Cross-sectional Norway | School of Dentistry, University of Copenhagen, Dental Department, Rigshospitalet | SS 16 (4) CG 27 (2) | SS 61.5 Aged CG 50 Young CG 24 | SS 87.5% CG 92.5% | pSS 16 European classification criteria (1993) | Examination, mirror test and oral smears |
| Patinen et al; 2004 | Oral Diseases | Cross-sectional Finland | - | CD+SS 20 (-) SS 20 (-) | CD+SS 61 SS 62 | 100% | pSS 40 AECG (2002) | WHO recommendation (1987) |
| Kosuki et al; 2004 | Oral Diseases | Cross-sectional Japan | Ichikawa General Hospital, Tokyo Dental College | SS 54 (0) CG 51 (0) | SS 58.09±10 .61 CG 50.98±15 .03 | - | Not determined. Fox criteria (1986) which fixed the AECG (2002) | Calibration trial between the examiner and patients and selective medium Candida Color |
| Mårtens et al; 2006 | Oral Diseases | Cross-sectional Hungary | University of Debrecen CG: Hajdú-Bihar County Dental Service | SS 49 (26) CG 43 (13) | SS 55±11 CG 49±15 | SS 93.8% CG 90.6% | pSS 49 AECG (2002) | Visual examination according to a standard procedure (Langlais et al., 1964) |
| Fox et al; 2008 | Journal of the American Dental Association | Cross-sectional USA | Nine Chauhan Hospital and Regional Dental Institute | (1) 277 (-) (2) 1225 (-) CG 606 (-) | (1) 62±12.6 CG 61±12.7 | (1) 90% (2) 93% CG 92% | pSS 1502 AECG (2002) | - |
| Olate et al; 2014 | International Journal of Rheumatology | Cross-sectional Chile | University of La Frontera, Hernán Henríquez Aravena Hospital | 35 (-) No CG | 53±15 | - | Not determined. Based on clinical and biopsy criteria | - |
| Blochowiak et al; 2016 | Advances in Dermatology and Allergology | Cross-sectional Poland | - | 40 (-) No CG | 28.25 | 94.5% | pSS 22 sSS 18 AECG (2002) | - |

(1) Studies which determine the prevalence of any type of oral lesions

(2) Studies which only determine the prevalence of Candida albicans oral lesions

| Author et al; Year | Journal | Type of study | Patients recruited at | Sample (Denture wearers) | Mean age (years) | Gender (F %) | Type of SS Classification criteria | Oral mucosal evaluation |
|--------------------|---------|---------------|-----------------------|--------------------------|-----------------|-------------|------------------------------------|------------------------|
| Tapper-Jones et al; 1980 | Journal of Clinical Pathology | Cross-sectional United Kingdom | Welsh National School of Medicine Dental School | SS 16 (11) CG 16 (11) | SS 57 CG 57 | SS 87.5% CG 87.5% | pSS 5 sSS 11 Bloch et al criteria (1965) | Examination, quantitative imprint culture technique |
| MacFarlane et al; 1984 | Microbiol | Cross-sectional United Kingdom | Glasgow Dental Hospital and School | SS 10 (9) CG 10 (9) | SS 62 CG 62 | SS 90% CG 90% | Not determined Bloch et al criteria (1965) | Clinical changes in the tongue (Bertran 1967) |
| Hernández et al; 1989 | Oral Surgery Oral Medicine Oral Pathology | Cross-sectional USA | Sjögren’s syndrome Clinic of the University of California | 246 (66) No CG | 52 | 87.8% | pSS 166 sSS 80 Bloch et al Criteria (1965) | Specific observation of Candida lesions |
| Lundström et al; 1995 | Clinical and Experimental Rheumatology | Cross-sectional Sweden | University Hospital, Linköping | 40 (15) No CG | 59 | 92.5% | pSS 40 Copenhagen criteria 1986 | Clinical oral examination, evaluation of subjective oral symptoms |
| Soto-Rojas et al; 1998 | Journal of Rheumatology | Cross-sectional Mexico | National Institute of Nutrition Salvador Zubirán | SS 50 (+) CG 31 (-) | pSS 56.9±11 sSS 47.4±13 CG 49.8±10 | pSS 95.2% sSS 96.5% CG 93.5% | pSS 21 sSS 29 Keratoconjunctivit is sicca, minor salivary gland biopsy, abnormalities in sialography /scintigraphy | WHO recommendation (1987) |
| Kindelan et al; 1998 | Oral Surgery Oral Medicine Oral Pathology | Cross-sectional United Kingdom | Charles Clifford Dental Hospital, Oral Medicine Clinic | 28 (10) No CG | pSS 56.9 sSS 56.6 | pSS 81.2% sSS 91.6% | pSS 16 sSS 12 European classification criteria of 1993 | - |
fulfill the eligibility criteria, were excluded (Appendix 1). Finally, 18 articles were included in our systematic review (3,9,11,15,19,21-30) (Fig. 1).

Study characteristics

Seventeen of the eighteen selected articles were cross-sectional studies and the other one was a cohort study. They were published between 1980 and 2016. A total of 3290 patients were studied: 2426 were SS patients (of which known: 2111 had pSS and 216 sSS), 3 of the studies did not specify the type of SS (MacFarlane et al., 10 SS patients; Koseki et al., 54 SS patients; and Olate et al., 35 SS patients), and 864 patients were CG (Table 1).

The mean age of the subjects ranged from 28.25-62 years in the SS group and 24-62 years in the CG (Table 1).

Regarding to gender, in the SS patients the female percentage ranged from 81.2% to 100%, and in the CG from 87.5% to 100%. Three articles did not specify the gender of the sample (12,28,30).

We did not consider the CG in Patinen et al. study, since they were celiac patients; neither in Kindelan et al. study (since they were xerostomic controls), nor Yan et al. (because they had oral candidiasis) (Table 1).

Main findings

The most frequent OL among SS patients was angular cheilitis, reported in fifteen of the eighteen selected papers. Atrophic glossitis was also common, reported in ten of the selected papers. Candida manifestations and recurrent or chronic oral ulcerations in eight of them; and grooves or fissuration of the tongue were reported in seven papers. None of the selected papers reflected the total prevalence within the SS or the CG patients (Table 2).

This is in accordance with what we found when compared to a CG. The types of OL which were significantly more common in SS are: angular cheilitis, (14,28) atrophic glossitis (9,28), grooves or fissuration of the tongue (9,14), clinical manifestation of candidiasis (14), erythematous candidiasis (28) and atrophic mucosa (28). Oral manifestations, with its respective percentages, both in SS and CG patients are recorded in Table 2.

Risk of bias in individual studies

Using the predetermined 10 domains for the methodological quality assessment according to the JBI (17), we determined ten of the selected papers (3,11,12,14,21,22, 25,26,29,30) to have a low quality assessment and eight of them (9,13,15,19,23,24,27,28) to have a high quality assessment. Table 3 shows a more detailed description of the articles included.

Risk of bias within studies

We detected some sources of information bias. First of all, different diagnosis criteria for SS have been used along the years. Second of all, some studies did not specify how the oral mucosal evaluation was carried out. Third of all, some studies did not specify if the patients were denture wearers. This could lead to overestimation or underestimation of the prevalence of OL.

Risk of bias across studies

Due to the fact that only articles published in English were reviewed, bias due to language publication could...
### Table 2. Oral manifestations in SS and CG.

| Study                          | Oral manifestations in SS and CG                                                                 |
|-------------------------------|--------------------------------------------------------------------------------------------------|
| Tapper-Jones et al; 1980      | Angular cheilitis: SS 18.7%, pSS 20%, sSS 18.1%, CG 0                                           |
|                               | Atrophic glossitis: SS 37.5%, pSS 40%, sSS 36.3%, CG 0                                         |
| Macfarlane et al; 1984        | Angular cheilitis: SS 30.0%, CG 0                                                                 |
|                               | Atrophic glossitis: SS 90.0%, CG 0                                                               |
| Hernández et al; 1989         | Angular cheilitis: SS 20%                                                                         |
|                               | Atrophic glossitis: SS 44%                                                                         |
|                               | Grooves/ Fissuration of the tongue: SS 52%                                                           |
|                               | Dorsal tongue erythema: SS 32%                                                                    |
|                               | Patchy erythema (nonlingual): SS 26%                                                               |
|                               | Removable white plaques: SS 1%                                                                      |
| Lundström et al; 1995         | Angular cheilitis: pSS 35%, sSS 75%                                                               |
|                               | Recurrent or chronic ulcerations: pSS 40%                                                           |
|                               | Oral lichenoid lesions: pSS 18%                                                                    |
|                               | Herpes labialis: pSS 2.5%                                                                         |
| Soto-Rojas et al; 1998        | Angular cheilitis: pSS 24%, sSS 24%, CG 0 (pSS vs CG p=0.017; sSS vs CG p=0.012)                 |
|                               | Atrophic glossitis: pSS 62%, sSS 76%, CG 16%                                                       |
|                               | Oral candidiasis: pSS 71%, sSS 76%, CG 23% (pSS vs CG p<0.001; sSS vs CG p<0.001)                  |
|                               | Grooves/ Fissuration of the tongue: pSS 62%, sSS 76%, CG 16% (pSS vs CG p<0.001; sSS vs CG p<0.001) |
|                               | Removable white plaques: pSS 4.76%, sSS 6.8%                                                        |
| Kindelan et al; 1998          | Angular cheilitis: pSS 6.2%, sSS 16.6%                                                             |
|                               | Atrophic glossitis: pSS 6.2%                                                                       |
|                               | Oral candidiasis: pSS 18.75%, sSS 25%                                                              |
|                               | Dorsal tongue erythema: sSS 8.3%                                                                    |
|                               | Erythematous candidiasis: sSS 8.3%                                                                  |
| Pedersen et al; 1999          | Angular cheilitis: pSS 18.7%, CG 0                                                                  |
|                               | Atrophic glossitis: pSS 68.7%, CG 0                                                                 |
|                               | Oral candidiasis: pSS 18.7%, CG 0                                                                   |
|                               | Recurrent or chronic ulcerations: pSS 25%                                                           |
|                               | Denture stomatitis: pSS 12.5%, CG 0                                                                  |
|                               | Mucosal friction: pSS 62.5%, CG 0                                                                    |
| Rhodus et al; 1999            | Oral candidiasis: SS 48%, CG 0                                                                      |
|                               | Angular cheilitis: SS 81%, CG 0                                                                     |
|                               | Removable white plaques: SS 14%, CG 0                                                                |
| Patinen et al; 2004           | Recurrent or chronic ulcerations: SS 30%, CD+SS 30%, Lennokladi: SS 35%, CD+SS 5%                 |
| Koseki et al; 2004            | Angular cheilitis: SS 44.5%, CG 2.0%                                                                 |
|                               | Atrophic glossitis: SS 16.7%, CG 13.5%                                                              |
|                               | Grooves/ Fissuration of the tongue: SS 33.3% 2.7%                                                   |
|                               | Shiny tongue: SS 16.7%, CG 0                                                                        |
|                               | Strawberry tongue: SS 5.6%, CG 0                                                                    |
| Leung et al; 2004             | Angular cheilitis: pSS 11.5%, sSS 12%, CG 0                                                          |
|                               | Atrophic glossitis: pSS 7.6%, sSS 8%, CG 0                                                            |
|                               | Removable white plaques: pSS 3.8%, sSS 4%, CG 0                                                        |
|                               | Erythematous candidiasis: pSS 3.8%, sSS 4%, CG 0                                                      |
| Márton et al; 2006            | Angular cheilitis: SS 2.04%, CG 4.0%                                                                  |
|                               | Atrophic glossitis: SS 3.4%, sSS 8%, CG 0                                                            |
|                               | Removable white plaques: pSS 3.8%, sSS 4%, CG 0                                                        |
|                               | Erythematous candidiasis: pSS 3.8%, sSS 4%, CG 0                                                      |
| Fox et al; 2008               | Recurrent or chronic ulcerations: PhysR-Pss 41%, SFS-PSS 46% (p<0.05)                              |
| Ergun et al; 2010             | Angular cheilitis: SS 21.6%, CG 0 (p=0.005)                                                           |
|                               | Atrophic glossitis: SS 48.6%, CG 10.8% (p=0.001)                                                      |
|                               | Recurrent or chronic ulcerations: SS 35.13%, CG 0                                                    |
|                               | Erythematous candidiasis: SS 62.16%, CG 13.5% (p=0.006)                                              |
|                               | Atrophic mucosa: SS 10.2%, CG 2.3%                                                                   |
| Yan et al; 2011               | Angular cheilitis: pSS 6.66%                                                                       |
|                               | Oral candidiasis: pSS 8%                                                                           |
|                               | Denture stomatitis: pSS 3.33%                                                                      |
|                               | Median rhomboid glossitis: pSS 6.6%                                                                  |
|                               | Dorsal tongue erythema: pSS 3.33%                                                                    |
| Likar-Manookin et al; 2013    | Oral candidiasis: 29.9%                                                                            |
|                               | Recurrent or chronic ulcerations: Recurrent aphthous stomatitis: 3.9%                                |
|                               | Chronic Ulcerative Stomatitis: 0.6%                                                                   |
|                               | Lichen planus: 7.1%                                                                                |
| Olate et al; 2014             | Angular cheilitis: 14%                                                                             |
|                               | Oral candidiasis: 3%                                                                               |
oral mucosal changes
(25%); and Patinen
differentiate between ulcers
study consider a young
(30%). Olate
- Main findings
We identified 18 studies reporting prevalence of oral
mucosal lesions in SS, 10 of them compared to a healthy
population. Not all the studies specified if such lesions were reported by a calibrated
(or always the same) examiner.

Discussion
- Summary of evidence
SS is known to be one of the most common rheumatic
diseases. To date, there is not a global overview of
which are the most common OL in these patients, nei-
ther if they appear more frequently in SS than in healthy
population.

- Main findings
We identified 18 studies reporting prevalence of oral
mucosal lesions in SS, 10 of them compared to a healthy
CG. We found surprising the young age of the patients.
This is due to Pedersen et al. study consider a young
CG, with a mean age of 24, and Blochowiak et al.2016
reported a young age of the patients: Lundström and Lindström reported a prevalence of
40%, which is in accordance with Fox et al. (43%);
Ergun et al. (35.1% of oral ulcerations in the SS group
vs 0% in the CG); Pedersen et al. (25%); and Patinen et al. (30%). Olate et al. differentiate between ulcers
(3%) and aphthae, with a higher prevalence: 31%; and
Blochowiak et al. classify them in non-specific ulcer-
ation (9.1% pSS, 22.2% sSS), small aphthae (13.6% pSS,
11.1% sSS), and Sutton’s aphthae (4.5% pSS, 0% sSS). In
these papers the possible aetiology of these ulcerations
was not given (Table 2, 2 continue).

Less frequently reported were oral lichenoid lesions (18-
35%) (11,26), herpes labialis (2.5%) (11) and oral mucos-
al friction (62%) (25).

- Secondary data
The increased prevalence of OL in SS may be due to
the impaired salivary gland function in these patients
(25). Proper levels of saliva allow for lubrication of the
mucosa, enhance healing of damage tissues, and play
an essential role in local immunity (10,15,19). Addition-
ally, Pedersen et al. found that oral mucosal changes
occurred more frequently in patients with the lowest
salivary flow rates.

It seems to be an inverse relationship between the rate
of salivary flow and the presence of candidiasis: low
levels of saliva are related to the presence of candidiasis
(12,15,29,30). Kindelan et al. and Yan et al. found a
significant inverse relationship between unstimulated sali-
vary flow and Candida infection. Pseudomembranous
candidiasis or removable white plaques was reported by
five authors (18,19,23,27,30). We found interesting the
fact that among SS patients pseudomembranous candi-
diasis was not common, with a prevalence range in the
cited articles of 0%-6.8%. Denture wearing is one of the
major predisposing factors for oral candidiasis, since
the fitting surface of the denture is the main reservoir

Table 2 continue. Oral manifestations in SS and CG.

| Condition                                | Prevalence in SS | Prevalence in CG |
|------------------------------------------|-----------------|-----------------|
| Recurrent or chronic ulcerations:         |                 |                 |
| Ulcers                                   | 3%              |                 |
| Aphthae                                   | 31%             |                 |
| Denture stomatitis:                       | 26%             |                 |
| Removable white plaques:                  | 0%              |                 |
| Erythematous candidiasis:                 | 3%              |                 |
| Non-specific ulceration:                  |                 |                 |
| Small Aphthae                             | pSS 13.6% sSS 11.1% |                 |
| Sutton’s aphthae                          | pSS 4.5% sSS 0  |                 |
| Grooves/ Fissuration of the tongue:       | pSS 4.5% sSS 0  |                 |
| Denture stomatitis:                       | pSS 4.5% sSS 0  |                 |
| Geographic tongue:                        | pSS 0 sSS 11.1% |                 |

CG=Control Group, SS=Sjögren syndrome, pSS=Primary SS, sSS=secondary SS, CD=Celiac Patients.

The association between SS and OL of autoimmune
aetiology remains unclear. Likar-Manookin et al. con-
ducted the first study of autoimmune oral diseases in
pSS. This study observed that 12.3% of pSS patients
presented autoimmune OL such as lichen planus (7.1%)
and recurrent aphthous stomatitis (3.9%). Chronic or re-
current ulceration seem to be common among SS pa-
tients: Lundström and Lindström reported a prevalence
of 40%, which is in accordance with Fox et al. (43%);
Ergun et al. (35.1% of oral ulcerations in the SS group
vs 0% in the CG); Pedersen et al. (25%); and Patinen et al. (30%). Olate et al. differentiate between ulcers
(3%) and aphthae, with a higher prevalence: 31%; and
Blochowiak et al. classify them in non-specific ulcer-
ation (9.1% pSS, 22.2% sSS), small aphthae (13.6% pSS,
11.1% sSS), and Sutton’s aphthae (4.5% pSS, 0% sSS). In
these papers the possible aetiology of these ulcerations
was not given (Table 2, 2 continue).

not be ruled out. Even though we searched four data-
bases, we cannot guarantee that some related papers
might not have been identified. Additionally, not all OL
were classified in the same way, and not all the studies
specified if such lesions were reported by a calibrated
(or always the same) examiner.

These tongue conditions, despite the discomfort that they cause, uncom-
monly require treatment.
Table 3. Risk of bias according to the JBI.

| Question                                                                 | Tapper Jones et al; 1980 | Mac Farlane et al; 1984 | Hernández et al; 1989 | Lundstrom et al; 1998 | Soto Rojas et al; 1998 | Kindelan et al; 1998 | Pedersen et al; 1999 | Rhodes et al; 1999 | Patimen et al; 2004 | Koseki et al; 2004 | Leung et al; 2004 | Marton et al; 2006 | Fox et al; 2008 | Ergun et al; 2010 | Yan et al; 2011 | Likar-Manookin et al; 2013 | Olate et al; 2014 | Blochowiak et al; 2016 |
|------------------------------------------------------------------------|--------------------------|--------------------------|-----------------------|-----------------------|-----------------------|-----------------------|---------------------|-------------------|---------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|-----------------------|------------------|------------------------|
| 1. Was the sample representative of the target population?              | Y                        | U                        | Y                     | Y                     | U                     | Y                     | Y                   | Y                 | Y                   | Y                 | Y                 | Y                 | Y                 | Y                 | Y                 | Y                     | Y                 | U                      |
| 2. Were study participants recruited in an appropriate way?             | U                        | Y                        | Y                     | U                     | U                     | U                     | U                   | U                 | U                   | Y                 | U                 | Y                 | Y                 | U                 | Y                 | U                        | Y                 | U                      |
| 3. Was the sample size adequate?                                       | U                        | U                        | Y                     | U                     | U                     | U                     | U                   | U                 | U                   | U                 | U                 | U                 | U                 | U                 | U                 | U                        | Y                 | U                      |
| 4. Were the study subjects and setting described in detail?            | Y                        | U                        | Y                     | N                     | Y                     | Y                     | Y                   | Y                 | Y                   | Y                 | Y                 | U                 | Y                 | U                 | U                 | N                        | Y                 | N                      |
| 5. Is the data analysis conducted with sufficient coverage of the identified sample? | U                        | Y                        | U                     | Y                     | Y                     | U                     | U                   | U                 | U                   | Y                 | Y                 | Y                 | Y                 | U                 | Y                 | Y                        | Y                 | N                      |
| 6. Were objective, standard criteria used for measurement of the condition? | U                        | Y                        | U                     | U                     | U                     | Y                     | Y                   | U                 | U                   | Y                 | Y                 | U                 | Y                 | U                 | U                 | U                        | U                 | U                      |
| 7. Was the condition measured reliably?                                | U                        | U                        | U                     | U                     | U                     | U                     | U                   | Y                 | U                   | U                 | U                 | U                 | U                 | U                 | U                 | U                        | U                 | U                      |
| 8. Was there appropriate statistical analysis?                         | Y                        | Y                        | Y                     | Y                     | Y                     | Y                     | Y                   | Y                 | Y                   | Y                 | Y                 | Y                 | Y                 | Y                 | Y                 | Y                        | Y                 | U                      |
| 9. Are all the important confounding factors/ subgroups/ differences identified and accounted for? | U                        | U                        | U                     | U                     | U                     | U                     | U                   | U                 | U                   | U                 | U                 | U                 | U                 | U                 | U                 | U                        | U                 | Y                      |
| 10. Were subpopulation identified using objective criteria?            | U                        | U                        | Y                     | U                     | U                     | Y                     | Y                   | U                 | Y                   | Y                 | Y                 | Y                 | Y                 | Y                 | U                 | Y                        | U                 | Y                      |

Y=Yes, N=No, U=Unclear, N/A=Not applicable.
of the yeast (28). Nevertheless, neither Soto-Rojas et al. nor Pedersen et al. found a direct relationship between the presence of oral candidiasis and the use of dentures in SS patients.

Strength and limitations

In order to carry out this systematic review, we conducted a specific search strategy for study selection. We included only those studies reporting prevalence of OL within the SS patients and, when available, those that compared them with a healthy CG. The comparison of the studies was limited due to the high degree of heterogeneity of OL. Although four databases were searched, we cannot rule out having missed relevant studies, also due to publication bias.

Diagnosis criteria of SS have changed periodically among the years. Since we did not have publication time restriction, different diagnostic criteria has been analysed among the reviewed studies. This must be taken into consideration when interpreting the results.

Conclusions

In summary, the results of this systematic review showed that the prevalence of oral mucosal lesions in SS patients is higher than in non-SS patients. Angular cheilitis, oral manifestations of candidiasis, ulcerations, atrophic glossitis and grooves or fissuration of the tongue were the most reported lesions. When compared to a CG, the same lesions mention before appeared more frequently in SS patients. Some of these lesions (angular cheilitis, oral manifestation of candidiasis, groves or fissuration of the tongue) seem to be related to the impaired salivary gland function: low levels of saliva predispose to these kind of OL. Nevertheless, the relationship of other autoimmune OL as ulcerations remains unclear. This type of lesions may be directly attributed to SS and not necessary secondary results of the hyposialia. The clinician should know which the most frequent OL in SS patients are, in order to carry out dental protocols with the objective of preventing, diagnosing and treating them correctly, and therefore, improve the quality of life of SS patients.

Owing to the high degree of heterogeneity regarding the types of SS, diagnosis criteria of SS, and different diagnosis criteria of OL, it was difficult to compare the studies. In addition, the quality assessment showed the low quality of most of the existing studies. In our opinion, it is necessary to collect other risk factors in these types of studies such as alcohol or smoking habits, presence of removable prosthesis, oral status, systemic diseases, and drugs intake; considering that these factors could be also related to the presence of oral diseases. The majority of the studies reviewed, only determined the presence of Candida albicans oral manifestation. Therefore, we recommend that new studies in which a complete oral mucosal evaluation, looking for all possible OL ought to be carried out.

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Author contributions  
JS did the search analysis, designed the methodology, reviewed all the selected studies, extracted the data and wrote the paper. JG contributed to the methodology, data collection and extraction. RMLP solved differences with eligible studies and contributed to the conceptualization and writing of the original draft. MF, LC and GH helped with the supervision, review and writing of the final version of this paper.  

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Conflict of interest  
The authors declare that they have no conflict of interest.