Xerostomia and hyposalivation in association with oral candidiasis: a systematic review and meta-analysis

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Abstract

Introduction Several studies reported that hyposalivation was associated with a higher prevalence of oral *Candida* colonisation and oral candidiasis, and despite the correlation between these conditions, no previous systematic review was conducted to examine this relationship in its utmost depth.

Objectives This study aims to investigate the relationship between xerostomia, hyposalivation and oral candidiasis.

Search methods This systematic review and meta-analysis was conducted in February 2021 through an electronic search.

Data sources The electronic search was performed on PubMed, Scopus, Web of Science through Clarivate, Medline through Clarivate and Cochrane Library.

Data selection This systematic review and meta-analysis included cohort, observational nested case-control cohort studies, and studies of other designs providing the number of patients with and without xerostomia or hyposalivation crossed with the number of patients with and without oral candidiasis or oral *Candida* growth. Studies included were conducted on adult populations with no restriction to sex or race. Included studies should use a reliable diagnostic method for all conditions of interest.

Data extraction Results were obtained from the implementation of the search strategy and managed using the EndNote Web and Rayyan Qatar Computing Research Institute (QCRI). Quantitative data synthesis was performed using the Review Manager 5.4 software.

Results A total of 429 studies were identified by searching the databases, of which nine studies were included for qualitative and quantitative data synthesis. The analysis included 590 xerostomic patients and 697 controls subgrouped into two categories: *Candida* growth (207 patients and 195 controls) and oral candidiasis (383 patients and 502 controls). The *Candida* growth subgroup analysis shows that the xerostomic patients are at higher risk for oral *Candida* growth than controls (OR [95% CI] = 3.13 [2.02–4.86]) and the oral candidiasis subgroup analysis yields that xerostomic patients are at higher risk for developing manifest oral candidiasis than controls (OR [95% CI] = 2.48 [1.83–3.37]).

Conclusion Our study concludes that patients with xerostomia have a higher risk than non-xerostomic control groups of developing oral candidiasis and oral fungal growth. Major inter-study heterogeneity, however, may restrict confidence in the accuracy of our results, and caution should therefore be taken in interpreting the evidence. In caring for patients with hyposalivation, we recommend healthcare professionals consider the possible association between both conditions. Furthermore, we recommend further research with improved methodological qualities and more valid diagnostic methods.

Background

Saliva is considered an essential body fluid that is known for its action in lubricating the oral cavity, taste and digestion, maintaining teeth integrity, as well as its antibacterial activity,[1] and hence the deficiency of saliva can cause serious problems.[2] In order to tackle these issues, it is important first to expand on the two conditions of interest to our study: xerostomia and hyposalivation.

Xerostomia is either true, having deficiency or complete lack of salivary secretions, or pseudo xerostomia, which refers only to the subjective perception of one's dry mouth despite having normal salivary functions. The definition of xerostomia also includes the density of the salivary secretions, their evaporation, absorption, or swallowing. Xerostomia can result from several local or systemic insults, including medication, irradiation and other medical conditions.[3] However, hyposalivation, or salivary gland hypofunction, refers solely to decreased function of the salivary glands.[4]

The prevalence of xerostomia ranged between 0.9% and 64.8% in a meta-analysis performed on several studies with varying geographical distribution.[5] Another meta-analysis found that the prevalence of dry mouth was about 22%.[6] Hyposalivation, however, recorded a prevalence ranging between 30.47% and 33.39% among the elderly, according to the meta-analysis of Pina *et al*.[7]

Xerostomia can result in multiple clinical manifestations, including caries, halitosis, burning mouth, teeth loss and oral candidiasis.[8] According to the Centres for Disease Control and Prevention, oral candidiasis, in turn, can be defined as the over-multiplication of *Candida*, a fungus, in the oral cavity due to the occurrence of certain changes in the mouth media, which makes it more suitable for fungal growth.[9]

The burden of oral candidiasis is relatively high worldwide, especially among vulnerable groups; for example, children with HIV/AIDS recorded a prevalence of up to 88%.[10] Candidiasis was also notably higher in diabetic patients than in the general population.[11] Also, it was significantly higher among patients receiving irradiation than the non-irradiated.[12]

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Candidiasis can lead to a set of complications such as pharyngeal candidiasis, which in turn can lead to difficulty swallowing and breathing. It can also result in oesophagal candidiasis or even fatal systemic dissemination.[13]

The association between xerostomia and oral candidiasis has long been examined in the literature. Nadig *et al*. found a significant inverse relationship between salivary flow rate in cases of xerostomia and oral candidiasis. *Candida albicans* was found to be the most prevalent type.[14] This was also the case for Torres *et al*.; however, in the latter, candidiasis was more frequent among men than women.[15] The study of Billings et al. found that salivary gland dysfunction and autoimmunity are both independent predictors of oral candidiasis.[16] Non-albicans *Candida* species were also found to be correlated with xerostomia during the examination of patients undergoing radiotherapy for head and neck cancer.[17]

Despite the vital correlation between the two, no previous systematic review was conducted to examine this relationship in its utmost depth. Therefore, this study aims to investigate the relationship between xerostomia, hyposalivation and oral candidiasis. Xerostomia refers mainly to the subjective perception of one's dry mouth despite having normal salivary functions. Accordingly, this study included all study designs that provide the number of patients with and without xerostomia or hyposalivation crossed with the number of patients with and without oral candidiasis or oral *Candida* growth, and performed meta-analyses on clinically diagnosed hyposalivation and self-reported mouth dryness.

Study question

Are oral candidiasis or oral *Candida* growth more common in adult patients with dry mouth and salivary hypo-secretion compared to individuals with normal salivary flow rates?

Methodology

Study design

This is a systematic review and meta-analysis reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[18] The study followed an established PROSPERO protocol (ID: CRD42021235654).

Study duration

The study was conducted from 15 February–22 February 2021.

Studied conditions

Xerostomia or hyposalivation, defined as the subjective sensation of dry mouth resulting from reduced or absent saliva with or without qualitative changes of saliva.[3]

Oral candidiasis, defined as yeast/fungi infection of the genus *Candida* that develops on the mucous membranes of the mouth.[9]

Population

Adult patients with primary or secondary hyposalivation or xerostomia who have been assessed for oral *Candida* growth or oral candidiasis and used for the assessment of the association between hyposalivation or xerostomia with oral *Candida* growth or oral candidiasis.

Comparison

The association between the diagnosis with xerostomia or hyposalivation with oral *Candida* growth or oral candidiasis. All studies enrolled for our review include the number of patients with salivary hypo-secretion or dry mouth with oral *Candida* growth or oral candidiasis, number of patients with salivary hypo-secretion or dry mouth without oral candidiasis, number of patients without salivary hypo-secretion or dry mouth with oral *Candida* growth or oral candidiasis, and number of patients without salivary hypo-secretion or dry mouth without oral *Candida* growth or oral candidiasis. Pooled random-effects meta-analysis was carried out to determine the odds ratio.

Control group

Sex- and age-matched individuals not diagnosed with hyposalivation, xerostomia, or other oral lesions were assumed as control groups for each of the included studies.

Main outcome

Odds ratios assessing the association between salivary hypo-secretion or dry mouth and oral candidiasis or oral *Candida* growth.

Selection criteria

Inclusion criteria

Cohort, observational nested case-control cohort studies, and studies of other designs providing the number of patients with and without xerostomia or hyposalivation crossed with the number of patients with and without oral candidiasis or oral *Candida* growth were included in this systematic review and meta-analysis

- Studies included were conducted on adult populations with no restriction on sex or race
- Included studies should use a reliable diagnostic method for all conditions of interest.

Exclusion criteria

- Case reports, reviews and interventional studies
- Studies not presenting the prevalence of hyposalivation or xerostomia crossed with oral candidiasis or oral *Candida* growth
- Studies with control groups diagnosed with other oral lesions.

Search strategy

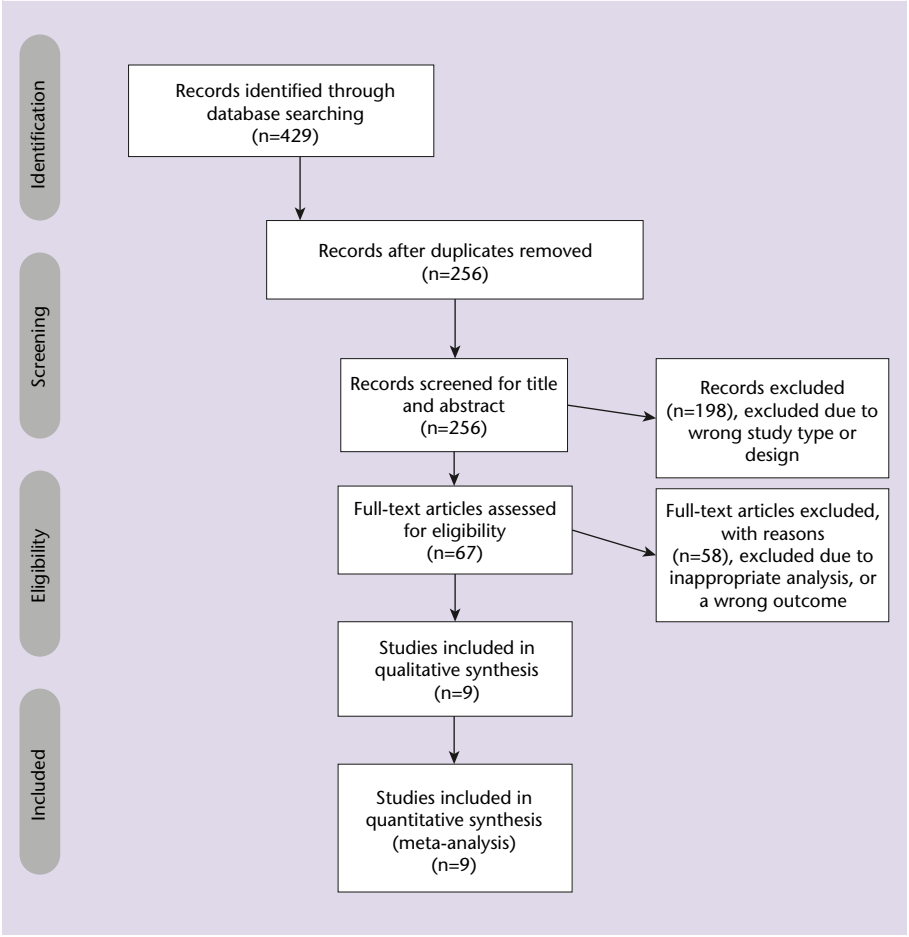
An electronic search was performed on PubMed, Scopus, Web of Science through Clarivate, Medline through Clarivate and Cochrane Library to gather the broadest range of relevant literature. No publication date restrictions were placed on search results within any of the databases used. Where possible, a common combination of defined MeSH and 'text word' entries, with Boolean operators, were used across each literary database. We filtered out non-human studies and studies involving participants <18 years of age where available.

We used the following queries to conduct our search.

For PubMed:

1. (Oral candidiasis[Title/Abstract] AND "Xerostomia"[MeSH Terms] AND "control"[Text Word])
2. ("oral candidiasis"[Title/Abstract] OR "oral thrush"[Title/Abstract]) AND "Xerostomia"[MeSH Terms] AND "control"[Text Word])
3. ("oral candidiasis"[Title/Abstract] OR "oral thrush"[Title/Abstract]) AND "Xerostomia"[Title/Abstract] AND "control"[Text Word])
4. ("oral candidiasis"[Title/Abstract] OR "oral thrush"[Title/Abstract]) AND ("Xerostomia"[Title/Abstract] OR "hyposalivation"[Title/Abstract]) AND "control"[Text Word])
5. ("candidiasis, oral"[MeSH Terms] AND "Xerostomia"[MeSH Terms]) AND (control group[Text Word]).

Fig. 1 PRISMA flow diagram summarising the search results



For Scopus:

- (TITLE-ABS-KEY (oral AND candidiasis) OR TITLE-ABS-KEY (oral AND thrush)) AND (TITLE-ABS-KEY (xerostomia) OR TITLE-ABS-KEY (hyposalivation) OR TITLE-ABS-KEY (sjögren's AND syndrome) OR TITLE-ABS-KEY (salivary AND hyposecretion)) AND ALL (control AND group).

For Web of Science through Clarivate:

- TS=((Xerostomia OR hyposalivation*) AND (oral candidiasis OR oral thrush*) AND control).

For Medline through Clarivate:

- ((TOPIC: (xerostomia*) AND TOPIC: (oral candidiasis*)) AND TOPIC: (control*)).

For Cochrane Library:

- #1 "xerostomia" in All Text AND "oral candidiasis" in Title Abstract Keyword AND control in All Text.

Data extraction

Results obtained from the implementation of the search strategy were tested for duplication using the EndNote Web and Rayyan Qatar Computing Research Institute (QCRI)[19] duplication evaluation features, followed by manual removal of undetected duplicates. Screening of pooled search results was carried out by two reviewers according to the inclusion and exclusion criteria to test titles and abstracts for suitability. Two reviewers conducted the full-text assessment of studies matching the initial screening requirements. Through the authors' debate, any difference in eligibility was overcome.

Two authors conducted the data extraction from studies following the full-text assessment. We extracted data relating to authors, study year, study design, study setting, study population, participant number, available data on participants' age and gender, a diagnostic method for hyposalivation or xerostomia, diagnostic method for oral *Candida* growth or oral candidiasis, number of patients with hyposalivation or xerostomia with oral *Candida* growth or oral candidiasis, number of patients with hyposalivation or xerostomia without oral *Candida* growth or oral candidiasis, number of patients without hyposalivation or xerostomia with oral *Candida* growth or oral candidiasis, number of patients without hyposalivation or xerostomia free of oral *Candida* growth or oral candidiasis, additional data on subgroups or special populations, and additional notes.

Risk of bias assessment

Newcastle-Ottawa quality assessment scale for case-control and cohort studies[20] was used to assess the quality of studies included for qualitative and quantitative data synthesis. The methodological risk of bias was assessed by two authors and conflicts were resolved through author debate.

Strategy for data synthesis

In order to provide a qualitative overview of included research characteristics and outcome data, summary tables were produced describing the gathered data from the included studies. A qualitative synthesis of the described data was conducted regardless of the feasibility of pooling the studies into the meta-analyses. Studies that follow full-text inclusion requirements but do not have odds ratio (OR) data were not included in the meta-analysis but were evaluated qualitatively.

We used Review Manager 5.4[21] to conduct the quantitative data synthesis for studies presenting case and control data on both conditions of interest. Fixed-effects meta-analyses were used to assess the association between hyposalivation or xerostomia and oral *Candida* growth or oral candidiasis. Subgroup analysis was conducted among studies associating hyposalivation and xerostomia with the incidence of oral candidiasis or *Candida* growth. Besides, subgroup analysis was conducted associating hyposalivation or xerostomia and oral *Candida* growth and clinically diagnosed oral candidiasis. Heterogeneity was assessed using an I2 statistic as part of the pooled meta-analysis. Publication bias was assessed using visual inspection of the funnel plot.

Results

Search results

A total of 429 studies were identified by searching the databases, of which 89 were imported from PubMed, 172 from Scopus, 48 from Web of Science through Clarivate, 114 from Medline through Clarivate and 6 from Cochrane. Eighty-one duplicates were removed using EndNote Web and 92 by the manual screening of similar

Table 1 Characteristics of the included studies

Study	Study year	Study design	Population type	Number of participants	Age range	Age (mean ± SD)	Men (n)	Men (%)	Country	Condition	Diagnosis of condition	Diagnosis of candida growth/ candidiasis	NOS score	(Events, total patients, events, total control)	OR (95% CI)
Arruda *et al.*[22]	2014	N/A	Patients with healthy control	44	45–90	56	18	40.9	Brazil	Hyposalivation	SFR using unstimulated (resting) whole saliva	Culture smear	7	(4, 10, 1 ,13)	8.00 (0.73, 88.23)
Belazi *et al.*[23]	2005	Case-control	Patients with T2DM	128	N/A	54 ± 7	68	53.1	Greece	Xerostomia	N/A	Microscopic examination of tissue scrapings from the oral mucosa*	7	(42, 66, 40, 62)	0.96 (0.47, 1.98)
			Healthy subjects	84	N/A	N/A	N/A	-		Xerostomia				(16, 24, 18, 60)	4.67 (1.70, 12.84)
Buranarom *et al.*[24]	2018	N/A	Independent dentate elders	53	N/A	71.9 ± 6	8	15.1	Thailand	Hyposalivation	CODS	Culture smear	7	(15, 22, 10, 31)	4.50 (1.39, 14.52)
Cunha *et al.*[25]	2015	Case-control	Neurofibromatosis 1	49	N/A	42.5 ± 14.8	14	28.5	Brazil	Hyposalivation	By calculation, the salivary flow rate	Clinical and cytopathology exam	6	(7, 29, 4, 20)*	1.27 (0.32, 5.09)
Nittayananta *et al.*[26]	2010	Cross-sectional	HIV patients and controls	135	18–63	32.9	77	57	Thailand	Hyposalivation	Clinical examination and measuring saliva flow rate	Oral rinse specimens	7	(15, 63, 9, 70)	2.12 (0.85, 5.26)
										Xerostomia				(11, 51, 13, 82)*	0.45 (0.20, 1.01)
Rhodus *et al.*[27]	1999	Case-control	Patients with Sjögren's syndrome and healthy controls	41	37–79	56.3	1	2.4	USA	Xerostomia	Clinical examination	Clinical examination	7	(22, 27, 0, 14)	118.64 (6.09, 2,310.94)
Serrano *et al.*[28]	2020	Cross-sectional	Patients with primary Sjögren's syndrome	61	N/A	57.64 ± 13.52	1	1.6	Spain	UWS hyposalivation	Clinical examination	Clinical examination	7	(7, 37, 1, 24)*	5.37 (0.62, 46.75)
										SWS hyposalivation				(7, 34, 1, 27)*	6.74 (0.77, 58.65)
Shinozaki *et al.*[29]	2006–2009	Case-control	Patients with xerostomia and controls	73	N/A	61.4 ± 8.1	4	5.4	Japan	Xerostomia	Clinical examination	Oral swabs and cultural examination	7	(31, 58, 2, 15)	7.46 (1.54, 36.07)
Suryana *et al.*[30]	2016–2019	Case-control	HIV patients and controls	448	18–60	35.9 ± 8.9	293	65.4	Indonesia	Xerostomia	N/A	Clinical examination	7	(114, 169, 93, 279)*	4.15 (2.76, 6.23)

Key:
* = studies reporting clinically manifest oral candidiasis.
SFR = salivary flow rate; T2DM = type II diabetes mellitus; UWS = unstimulated whole saliva; SWS = stimulated whole saliva; CODS = condition of dry mouth sign (at least 1 of 10 signs of the dry mouth sticking of an intraoral mirror to the oral mucosa or tongue, frothy saliva, no saliva pooling in the mouth floor, loss of papillae of the tongue dorsum, altered gingival architecture, the glassy appearance of the oral mucosa, lobulated fissured tongue, cervical caries and mucosal debris on the palate).

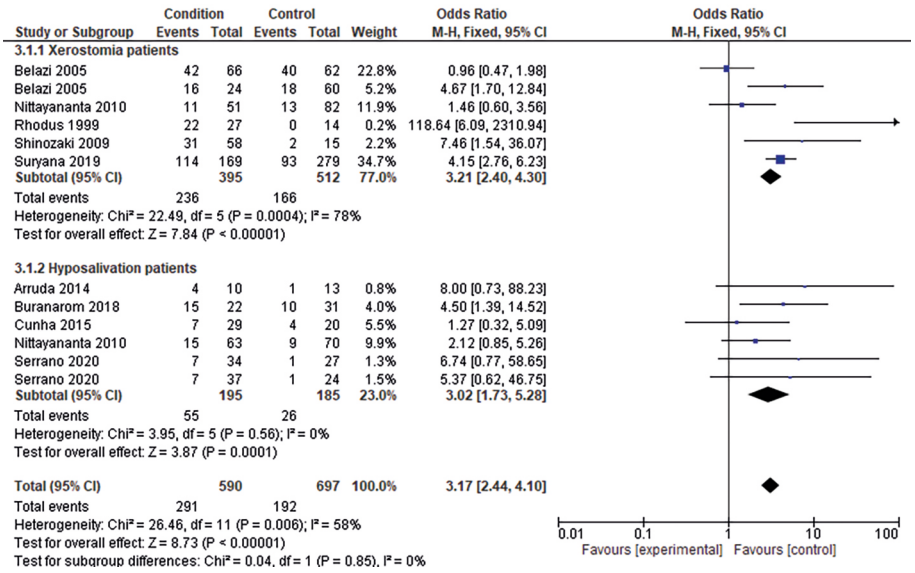


Fig. 2 Forest plot that shows the association between xerostomia and hyposalivation and oral candidiasis and *Candida* growth

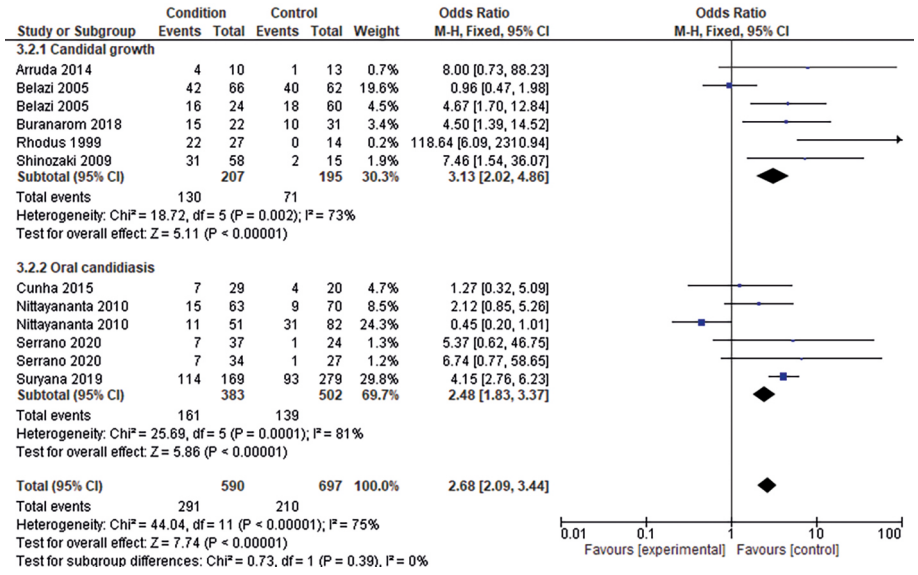


Fig. 3 Forest plot of the association between xerostomia and oral candidiasis

study titles on Rayyan QCRI. After duplicate removal, 256 studies were enrolled for the title and abstract screening, of which 198 were excluded, and 67 studies were enrolled for full-text assessment, 58 of which were excluded due to wrong outcome or inappropriate analysis as most of them did not exactly report the association between the diagnosis with xerostomia, or hyposalivation with oral *Candida* growth or oral candidiasis, and some others did not associate between the prevalence of xerostomia and oral *Candida* growth, and nine studies were included for qualitative and quantitative data synthesis. See the summary of search results in Figure 1.

Characteristics of the included studies

A total of nine studies were included for the qualitative and quantitative data synthesis[22,23,24,25,26,27,28,29,30] conducted from 1999[30] to 2020[28] with a total of 1,287 participants. Disease-restricted populations were patients with type 2 diabetes mellitus (T2DM),[23] neurofibromatosis 1 (NF1) patients,[25] HIV-positive subjects[26,30] and patients with Sjögren's syndrome.[27,28] Clinically manifest oral candidiasis was reported by four studies,[25,26,28,30] whereas the remaining data was based on positive *Candida* swab and/or culture results among patients and controls. Regarding the risk of bias assessment, all of the included studies did not provide a response rate of the participants and one study[24] did not appropriately define the control group. Table 1 summarises the characters of the included studies.

Xerostomia and hyposalivation in association with oral candidiasis and Candida *growth*

This analysis shows that xerostomic patients are at greater risk of developing oral candidiasis or *Candida* growth than the control group (OR [95% CI] = 3.21 [2.40–4.30]). Patients with hyposalivation were at higher risk of developing oral candidiasis or *Candida* growth than the control group (OR [95% CI] = 3.02 [1.73–5.28]) (Fig. 2).

Oral Candida *growth and oral candidiasis in association with hyposalivation or xerostomia*

The analysis evaluating the association between xerostomia or hyposalivation and oral candidiasis included 590 patients and 697 controls sub-grouped into two categories: *Candida* growth (207 patients and 195 controls) and oral candidiasis (383 patients and 502 controls).

The diagnosis of oral candidiasis is primarily clinical. When the clinical diagnosis requires confirmation, establishing a microbiological diagnosis with other diseases, cases defined by antifungal treatment resistance, and in hyperplastic candidiasis, biopsies are taken, a microbiological diagnostic is undertaken.[31]

The *Candida* growth subgroup analysis shows that the xerostomia or hyposalivation patients are at higher risk for oral *Candida* growth than controls (OR [95% CI] = 3.13 [2.02–4.86]). Similarly, the oral candidiasis subgroup analysis yields that xerostomia or hyposalivation patients are at higher risk for developing manifest oral candidiasis than controls (OR [95% CI] = 2.48 [1.83–3.37]) and with an overall OR (95% CI) = 2.68 (2.09–3.44) (Fig. 3).

Heterogeneity and publication bias

Publication bias was assessed by visual inspection of the funnel plot (Fig. 4). Visual inspection reveals symmetrical distribution of the OR obtained from the studies. Significant inter-study heterogeneity was found among the *Candida* growth studies (I2 = 73%), whereas the I2 for the oral candidiasis subgroup was 81% with an overall I2 = 75%.

Discussion

From the evidence reviewed and analysed from the included studies, we found that patients with xerostomia are at greater risk of developing oral candidiasis or *Candida* growth than the control group (OR [95% CI] = 3.21 [2.40–4.30]). Up to the authors' knowledge, no systematic reviews and meta-analyses were conducted assessing the association between hyposalivation and oral candidiasis. Therefore, we provide the best picture of how these two conditions affect each other in terms of risk. The predefined rigorous search criteria, as well as accurate selection and assessment of methodological quality for each study, add to the strengths of this study; however, high heterogeneity limits the confidence in the precision of the findings. The variety of study designs, populations, as well as diagnostic and examination criteria can attribute to the between-study heterogeneity.

Nittayanata *et al*.[26] reported that the incidence of oral candidiasis appears to be influenced by xerostomia and disease progression in particular. However, they found no correlation between hyposalivation and the prevalence of oral candidiasis. Another study found a high prevalence of mixed *Candida* colonisation and oral candidiasis in patients with xerostomia. The colony-forming unit (CFU) count, which was negatively correlated with the SWS and UWS, was linked to the severity of oral candidiasis. These findings indicate that hyposalivation induced a higher number of *Candida*, which resulted in more extreme oral candidiasis.[29]

In the present study, patients with hyposalivation were at higher risk of developing oral candidiasis or *Candida* growth than the control group (OR [95% CI] = 3.02 [1.73–5.28]). Buranarom *et al*. reported a higher prevalence rate of *Candida* colonisation among patients with hyposalivation (p = 0.010; adjusted OR = 4.36). They also found significant negative associations between salivary flow rates and the amount of *Candida* in the oral cavity.[24] Many previous studies also reported that a declined salivary flow rate is considered a risk factor regarding *Candida* colonisation.[15,32]

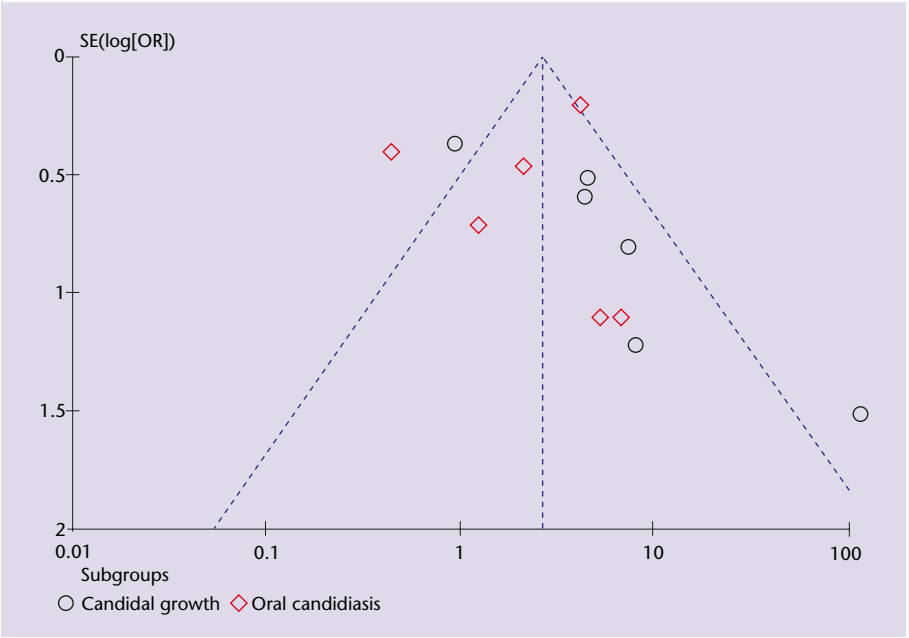
We found that hyposalivation or xerostomia patients are at risks for oral *Candida* growth and clinical oral candidiasis (OR [95% CI] = 3.13 [2.02–4.86] and 2.48 [1.83–3.37], respectively), with an overall pooled OR for both conditions of 2.68 (2.09–3.44). There is a higher risk for *Candida* growth of oral candidiasis among xerostomic and salivation patients in all groups from individual studies included in our meta-analysis except for two groups of disease-restricted populations.[23,26] Whole stimulated salivary flow rates were inversely correlated with mean *Candida* density as found in the studies of Radfar *et al*.,[33] Tapper-Jones *et al*.[34] and Torres *et al*.[15] The study by Radfar *et al*. on 103 Sjogren's syndrome patients showed that oral *Candida* load was negatively associated with a low stimulated salivary flow rate and not a low unstimulated salivary flow rate (P ≤0.0001).[33] On the other hand, some studies have not found an association between *Candida* CFU counts and whole stimulated or unstimulated salivary flow rates in the carriage state or among healthy subjects, but only in the infection state, a negative correlation between these parameters was found.[15,35]

Regarding disease-restricted populations, the subjects included in the Belazi *et al*. study were T2DM patients. The study revealed an OR of 0.96 (0.47–1.98) for oral *Candida* growth;[23] however, the certainty of the findings of this study is limited due to the small sample size, as the confidence intervals widely extend. A case-control study by Obradović *et al*. examining the frequency of oral candidiasis among diabetic and control groups found that candidiasis was significantly lower among the control group.[36] Another study that associated diabetic control with oral candidiasis found that glycosylated haemoglobin (HbA1c) >12% was highly predictive of oral *Candida* infection in diabetic patients.[37] This can be attributed to the predisposition of diabetic individuals to oral fungal growth and oral candidiasis.

Oral candidiasis is the most common fungal infection among immunocompromised patients as it occurs in up to 95% of HIV-infected individuals during their illness as the defective salivary antifungal activity may contribute to the *Candida* growth in patients with AIDS.[38,39] Using the data from the study of Nittayanata *et al*. that was conducted among HIV patients and controls, the OR for contracting oral candidiasis among patients suffering from hyposalivation and xerostomia was 2.12 (0.85–5.26) and 0.45 (0.20–1.01), respectively. The authors, however, did not find a significant difference for hyposalivation (P = 0.101) or xerostomia (P = 0.405) in association with oral candidiasis, which they attributed to the small sample size. Of interest, the authors found a significant association between hyposalivation and CFU of *Candida* (P = 0.010), but not with xerostomia (P = 0.282).[26] Likewise, the study of Suryana *et al*. aimed to identify risk factors of oral candidiasis among people living with HIV/AIDS and used a larger sample size (n = 448). The study found people living with HIV/AIDS with xerostomia to be at higher risk of developing oral candidiasis (OR = 4.15 [2.76–6.23], P = 0.000).[30]

The study of Cunha *et al*. evaluated the salivary flow rate in subjects with NF1 compared to sex- and age-matched controls.

Fig. 4 Funnel plot of heterogeneity and publication bias



Hyposalivation was diagnosed in 29 (59%) and oral candidiasis was diagnosed in 11 (22%) of the NF1 individuals. Of these 11, seven subjects had hyposalivation (OR = 1.27 [0.32–5.09]). The authors believe that the high prevalence of hyposalivation among NF1 subjects can be attributed to the salivary gland alterations caused by the NF1 gene mutations.[25]

This review included different population types with matched; however, it is of importance that untreated or undiagnosed xerostomic individuals might have a higher risk for oral *Candida* growth or oral candidiasis. Therefore, the presence or absence of these conditions combined can be under-reported.

Limitations

Publication bias may still occur. Despite the fact that this systematic review covered a vast range of publications in the search process, it may not contain all studies with data relevant to our studies, since studies with positive findings indexed inside search databases are easier to find. Besides, observational research designs are not the best way to determine the causal association between an intervention and an outcome since certain characteristics vary or alter over time among intervention groups. As a result, including observational studies in this meta-analysis could result in bias in the summary effect. Another limitation to this study was the ability to generate evidence by pooling data from studies with different diagnostic methods and cut-off values. In order to produce adequate data on the association of oral candidiasis and hyposalivation, more primary studies should therefore be conducted.

Conclusion and recommendations

Patients with xerostomia and hyposalivation were found at greater risk of developing oral candidiasis than the control groups; however, the hazard of xerostomic patients was slightly higher than those with hyposalivation. Xerostomia or hyposalivation patients have a higher chance of developing oral candidiasis and oral fungal growth than non-xerostomic control groups. However, significant between-study heterogeneity might limit the confidence of the precision of our findings and caution interpreting the data should therefore be taken. We recommend healthcare professionals consider the potential association between both conditions when caring for patients with hyposalivation. In addition, we recommend researchers conduct more studies with enhanced methodological qualities and more valid diagnostic tools.

Ethics declaration

The authors declare no conflicts of interest.

Author contributions

Dr Molek: searching strategy, methodology and result. Prof Dr I. Nyoman Ehrich Lister: data extraction and statistic analysis. Dr Florenly: filtering studies included and quality appraisal of studies. Dr Tuka Abdul Wahab: introduction, data extraction. Dr Clarissa Lister: filtering studies included and quality appraisal of studies. Dr Fioni: designed/planning/ idea of the paper led to submission, team leader, searching strategy, approved the final version, revised manuscript.

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