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Non-dental oral cavity findings in gastroesophageal reflux disease: a systematic review and meta-analysis

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ABSTRACT

Gastroesophageal reflux disease (GERD) is known as the most prevalent gastrointestinal disorder in the United States, leading to substantial morbidity, although associated mortality is rare. Based on the appearance of esophageal mucosa on upper endoscopy, GERD is divided into erosive esophagitis (ERD) and nonerosive reflux disease (NERD). Heartburn and acid regurgitation are the typical symptoms of the disease, although some patients may present atypical manifestations such as epigastric pain, nausea, asthma, chronic cough, pharyngitis, laryngitis, sleep disturbances, otitis, and sinusitis. Other signs, such as oral mucosal lesions may result from GERD by direct acid or acidic vapor contact in the oral cavity. Oral manifestations such as tooth erosion, periodontitis, gingivitis, palatal erythema, ulceration, glossitis, oral acid burning sensation, halitosis, xerostomia have recently been reported in GERD patients. A considerable percentage of the patients are affected by oral manifestations before the onset of gastrointestinal symptoms, although in most cases the gastrointestinal signs and symptoms dominate the clinical picture. The injured oral mucosa negatively impacts the quality of life, especially functional limitation, physical inability and psychological disabilities, thus leading to social isolation. There is plenty of non-standardized information on the oral mucosal changes in GERD. In this context, we aimed at synthesizing and analyzing the current available evidence on non-dental oral cavity lesions and complaints that are present in patients diagnosed with GERD.

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non-dental oral cavity, gastroesophageal reflux, systematic review, meta-analysis

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Introduction

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of the stomach contents causes troublesome symptoms and/or complications [1]. GERD is known as the most prevalent gastrointestinal disorder in the United States, leading to substantial morbidity, although associated mortality is rare [2]. Based on the appearance of the esophageal mucosa on upper endoscopy, GERD is divided into erosive esophagitis (ERD) and nonerosive reflux disease (NERD) [3]. Heartburn and acid regurgitation are the typical symptoms of the disease, although some patients may present atypical manifestations such as epigastric pain, nausea, asthma, chronic cough, pharyngitis, laryngitis, sleep disturbances, otitis, sinusitis [4]. Other signs, such as oral mucosal lesions may result from GERD by direct acid or acidic vapor contact in the oral cavity. The oral manifestations, such as tooth erosion, periodontitis, gingivitis, palatal erythema, ulceration, glossitis, oral acid burning sensation, halitosis, xerostomia have recently been reported in GERD patients [5]. A considerable percentage of the patients are affected by oral manifestations before the onset of the gastrointestinal symptoms, although in most cases the gastrointestinal signs and symptoms dominate the clinical picture [6]. The injured oral mucosa negatively impacts the quality of life, especially functional limitation, physical inability and psychological disabilities, thus leading to social isolation [7]. There is plenty of non-standardized information on oral mucosal changes in GERD [8]. In this context, we aimed at synthesizing and analyzing the current available evidence on non-dental oral cavity lesions

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and complaints that are present in patients diagnosed with GERD.

Discussions

This review with meta-analysis is grounded in a structured protocol, developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) [9,10].

Research strategy. PubMed, Web of Science, Science Direct, Embase and Cochrane Library were searched by two independent researchers using a pre-piloted screening and selection tool in order to identify the eligible studies published between January 2000 and June 2020. The search was based upon Medical Subjective Heading (Mesh) terms of “Mouth Diseases” and "Gastroesophageal Reflux" (Table 1).

All articles relevant to the topic of this paper were retrieved and their bibliographies were hand searched for further references.

The screening and selection process consisted of two stages: 1) screening of title and abstracts and 2) screening and selection of full text papers (Figure 1).

Table 1. Search strategy

PubMed
("Mouth Diseases"[Mesh]) AND "Gastroesophageal Reflux"[Mesh]
Web of Science
("Behcet Syndrome" OR “Bell Palsy" OR “Burning Mouth Syndrome” OR “Candidiasis, Oral” OR “Dry Socket” OR “Facial Hemiatrophy” OR “Facial Nerve Diseases” OR “Bell Palsy” OR “Facial Hemiatrophy” OR “Facial Nerve Injuries” OR “Facial Neuralgia” OR “Herpes Zoster Oticus” OR “Melkersson-Rosenthal Syndrome” OR “Mobius Syndrome” OR “Facial Paralysis” OR “Focal Epithelial Hyperplasia” OR “Granulomatosis, Orofacial” OR “Hemifacial Spasm” OR “Leukoedema, Oral” OR “Lichen Planus, Oral” OR “Lip Diseases” OR “Cheilitis” OR “Cleft Lip” OR “Herpes Labialis” OR “Lip Neoplasms” OR “Ludwig's Angina” OR “Melkersson-Rosenthal Syndrome” OR “Mouth Abnormalities” OR “Cleft Lip” OR “Cleft Palate” OR “Fibromatosis, Gingival” OR “Macrostomia” OR “Microstomia” OR “Velopharyngeal Insufficiency” OR “Mouth Neoplasms” OR “Gingival Neoplasms” OR “Leukoplakia” OR “Lip Neoplasms” OR “Palatal Neoplasms” OR “Salivary Gland Neoplasms” OR “Tongue Neoplasms” OR “Edentulous” OR “Mucositis” OR “Noma” OR “Oral Fistula” OR “Dental Fistula” OR “Oroantral Fistula” OR “Salivary Gland Fistula” OR “Oral Hemorrhage” OR “Gingival Hemorrhage” OR “Oral Manifestations” OR “Oral Submucous Fibrosis” OR “Oral Ulcer” OR “Periodontal Diseases” OR “Furcation Defects” OR “Gingival Diseases” OR “Peri-Implantitis” OR “Periapical Diseases” OR “Periodontal Atrophy” OR “Periodontal Cyst” OR “Periodontitis” OR “Tooth Loss” OR “Tooth Migration” OR “Tooth Mobility” OR “Ranula” OR “Salivary Gland Diseases” OR “Mikulicz' Disease” OR “Parotid Diseases” OR “Salivary Calculi” OR “Salivary Gland Fistula” OR “Salivary Gland Neoplasms” OR “Sialadenitis” OR “Sialometaplasia” OR “Sialorrhea” OR “Submandibular Gland Diseases” OR “Xerostomia” OR “Stomatitis” OR “Stevens-Johnson Syndrome” OR “Vesicular Stomatitis” OR “Tongue Diseases” OR “Glossalgia” OR “Glossitis” OR “Glossoptosis” OR “Macroglossia” OR “Tongue Neoplasms” OR “Oral Tuberculosis”) AND (“Gastric Acid Reflux” OR “Acid Reflux Gastric” OR “Reflux Gastric Acid” OR “Gastric Acid Reflux Disease” OR “Gastro-Esophageal Reflux” OR “Gastro Esophageal Reflux” OR “Reflux Gastro-Esophageal” OR “Gastroesophageal Reflux Disease” OR “GERD” OR “Reflux Gastroesophageal” OR “Esophageal Reflux” OR “Gastro- oesophageal Reflux” OR “Gastro oesophageal Reflux” OR “Reflux Gastro-oesophageal”)
Science Direct
("gastroesophageal reflux" OR "Gastric Acid Reflux") AND ("oral disease" OR "oral lesion" OR "mouth disease" OR "mouth lesion")
Embase
('gastroesophageal reflux' OR 'gastric acid reflux') AND ('mouth disease' OR 'mouth lesion’ OR 'oral disease' OR 'oral lesion')
Cochrane Library
('gastroesophageal reflux' OR 'gastric acid reflux') AND ('mouth disease' OR 'mouth lesion’ OR 'oral disease' OR 'oral lesion')

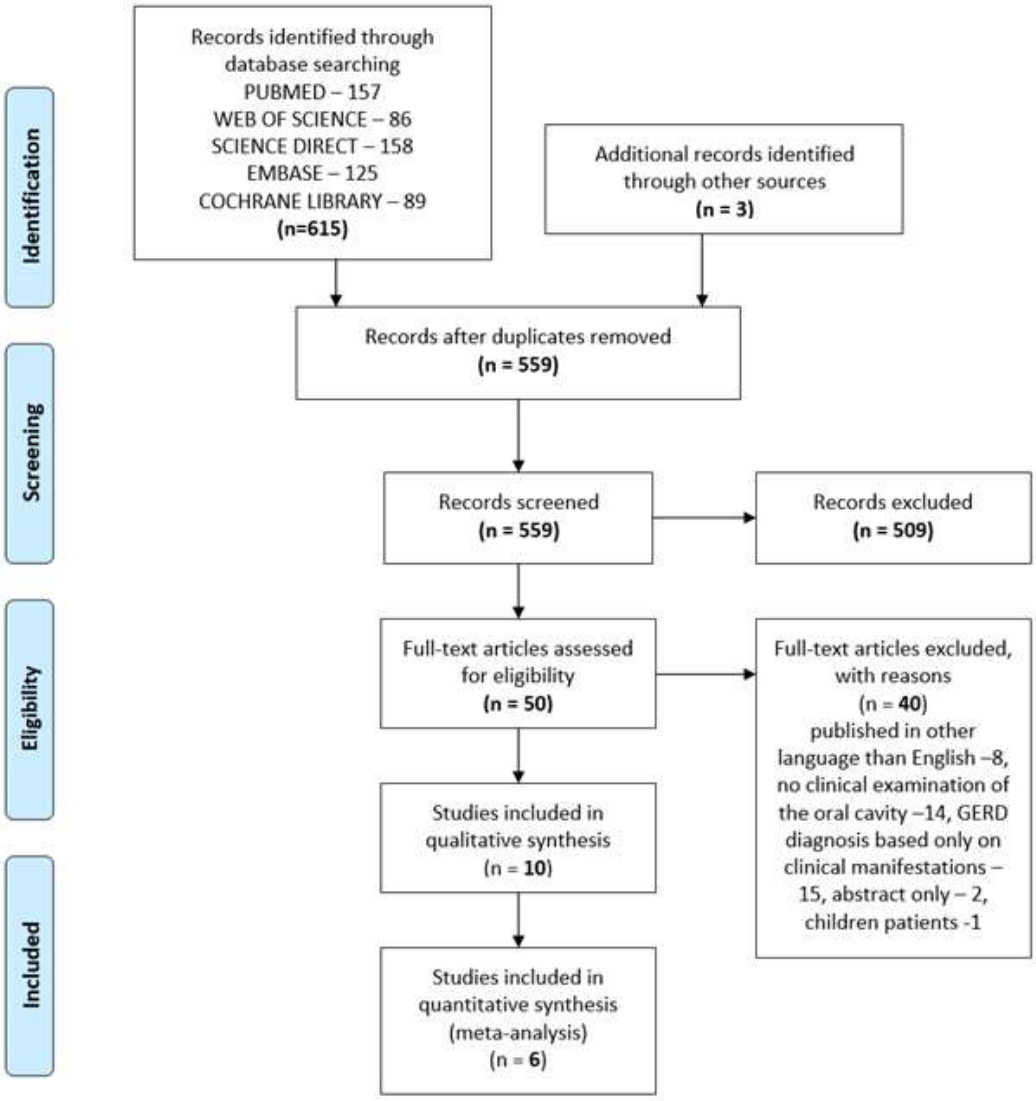

Figure 1. PRISMA Flow Diagram

Inclusion and exclusion criteria. The selected studies for the systematic review fulfilled the following criteria: (a) cross-sectional and case-control studies, (b) publications in English, (c) regardless of the publication status (published, in press, or in progress) (d) conducted on adults clinically diagnosed with GERD who underwent at least one additional evaluation for the confirmation of the diagnosis - upper gastrointestinal endoscopy, esophageal manometry or esophageal pH monitoring, (e) reporting results on the presence of non-dental oral cavity lesions or oral complaints. We excluded experimental studies, case presentations, case series, systematic reviews, articles published in other languages than English, or conducted among children populations.

The documents were handled using the Mendeley reference manager software. The selection process was conducted by two independent reviewers, while disagreements were settled by means of group discussions until a consensus was reached.

Data extraction. The data were extracted by two independent researchers using a pre-defined extraction form. Any disagreement between these two authors was resolved by means of group discussions. For each study, the following data were extracted: title, first author, year of publication, country, type of study, GERD diagnostic method, number of patients for the reported groups, gender, mean age, the use of PPI (proton pump inhibitor) therapy, reported exclusion criteria, data on the oral cavity assessment, type of lesion, type of complaint, odds ratio with confidence interval, mean plus standard deviation, p value.

Meta-analysis. For the studies reporting homogenous data, the relationship between the presence of GERD and a specific non-dental oral cavity lesion or a specific oral complaint was examined based on the odds ratio (OR) and its 95% confidence interval (CI). For studies measuring a specific score, the mean and standard deviation (SD) were used to calculate the standard mean difference (SMD) and

the 95% CI. Effect sizes were interpreted using Cohen's Standards for Interpreting Effect Sizes [11]. Assuming the differences in the methodology of the studies included in the meta-analysis, a random effect model was used. All calculations were conducted in the Comprehensive Meta-Analysis® software (v3).

The heterogeneity of the studies was analyzed using the I2 statistic, where a I2 ≥ 75% indicated important heterogeneity, with $p < 0.05$ defined statistical significance. Tau2 (τ2) was calculated using the restricted maximal likelihood method. Results showing important heterogeneity are reported in this article, but they cannot be used to generalize conclusions. The publication bias was analyzed using Egger's regression, with $p < 0.05$ defining statistical significance and funnel plots for graphical description. In the event of publication bias, the Rosenthal method was used to calculate the fail-safe N statistic.

Some of the studies included in the meta-analysis compared GERD patients to different control subgroups, younger and older controls [12,13]. This problem was solved by combining the two control subgroups to form a single one, according to Cochrane Guidelines [14]. Some studies calculated scores to define oral lesions/symptoms. The PMA Index (papillary marginal attachment index: P was defined as "any degree of inflammation of the interdental papilla mesial to the tooth"; M was defined as "any degree of inflammation of the marginal gingiva on the facial aspect"; A was defined as "any disturbance of attachment as indicated by any degree of recession of the marginal gingiva from normal contour") was used to define gingivitis in two studies [12,13] and Saxon test (simple, reproducible, and low-cost test for xerostomia, which involves chewing on a folded sterile sponge for 2 minutes; saliva production is quantitated by weighing the sponge before and after chewing and it was used to define xerostomia; normal control subjects produced greater than or equal to 2.75 gm of saliva in 2 minutes) in two studies [12,13]. Two of the studies [12,13] that quantify xerostomia measured the quantity of saliva in grams secreted in 2 minutes, while the other two in milliliters/minute [15,16]. The results were analyzed together, assuming that the difference in protocols were negligible.

Study inclusion. The systematic search provided a total of 615 citations (Figure 1). Three additional citations were identified by means of manually searching the relevant references for the field published papers. After eliminating the duplicates, 599 studies remained. Out of these, 509 were discarded because they did not meet the inclusion criteria. The full text of the remaining 50 citations was examined in detail. Forty full-text published studies did not meet the inclusion criteria and were excluded from the analysis. The reasons for exclusion were: published in other languages than English (n=8), no clinical examination of the oral cavity (n=14), GERD diagnosis based only on clinical manifestations (n=15), abstracts only (n=2), children patients (n=1). Experimental studies, case presentations, and case series were also excluded.

Ten studies were included for the narrative synthesis [12,13,15–22]. Two studies did not include a control group (healthy subjects) and were, therefore, excluded from the quantitative analysis [17,19]. Only one study reported periodontitis in both patients and healthy controls and was impossible to be analyzed quantitatively [18]. One study reported different measures of gingivitis and was consequently excluded from the meta-analysis [22]. Accordingly, 6 studies were deemed eligible for inclusion in the meta-analysis (Table 2).

Table 2. Studies included for the narrative synthesis

No.	First author, year	Country	GERD diagnosis	M (%)	F (%)	Age (mean ± SD)	Controls (heathy subjects) (%)	GERD (%)	ERD (%)	NERD (%)	Chronic/ severe GERD with DE	Mild GERD without DE	Reported lesion	Reported complaint	Citation
1.	Warsi I 2019	Pakistan	UGE	109 (58.3%)	78 (41.7 %)	41-60 (80%)	NA				66 (35.3%)	121 (64.7%)	AC, C, Gi, Gl, L, OSF, U	X	[17]
2.	**Watanabe M 2017**	**Japan**	**UGE, GF**	**57 (54.3%) (GERD)**	**48 (45.7%) (GERD)**	**66.4 ± 13.0 (GERD)**	**50 (32.3%)**	**105 (67.7%)**					**Gi, Gl, PE**	**X**	**[13]**
3.	Adachi A 2016	Japan	UGE	191 (68.2%)	89 (31.8 %)	52	257 (91.8%)		23 (8.2%)				P		[18]
4.	Deppe H 2015	Germany	UGE, pHm	30 (42.3%)	41 (57.7 %)	49.7 ± 15.1	NA	71 (100%)	29 (40.8%)	42 (59.1%)			Gl, P, PE		[19]

5.	**Yoshikawa H 2012**	**Japan**	**UGE**	**21 (52.5%) (GERD)**	**19 (47.5 %) (GERD)**	**68.8 (GERD)**	**30 (42.9 %)**	**40 (57.1%)**	**18 (45 %)**	**22 (55 %)**	**Gi, U**	**OABS, SH, X**	**[12]**
6.	**Corrêa MC 2012**	**Brazil**	**UGE, pHm, Ma**	**20 (33.3%)**	**40 (66.6 %)**	**33.41 (GERD)**	**30 (50 %)**	**30 (50%)**	**10 (33.3 %)**	**20 (66.6 %)**		**X**	**[15]**
7.	**Di Fede O 2008**	**Italy**	**UGE, pHm**	**89 (44.5%) (GERD)**	**111 (55.5 %) (GERD)**	**46.9 (M), 49.3 (F)**	**100 (33.3 %)**	**200 (66.6%)**			**PE**	**OABS, SH, X**	**[20]**
8.	**Campisi G 2008**	**Italy**	**UGE, pHm**	**58 (48.3%) (GERD)**	**62 (51.6 %) (GERD)**	**44.18 (M), 48.8 (F)**	**98 (45 %)**	**120 (55 %)**				**OABS, X**	**[16]**
9.	**Corrêa MC 2008**	**Brazil**	**UGE, pHm, Ma**	**41 (41 %)**	**59 (59 %)**	**35.5 ± 12.9**	**50 (50 %)**	**50 (50 %)**			**U**	**OABS**	**[21]**
10.	Muñoz JV 2003	Spain	UGE, pHm	71 (39.2%) (GERD)	110 (60.7 %) (GERD)	47.8 ± 14.1	72 (28.4 %)	181 (71.6%)			Gi		[22]

UGE- upper gastrointestinal endoscopy, GF- gastrointestinal fiberscope, pHm- esophageal pH monitoring, Ma – esophageal manometry, GERD- gastroesophageal reflux disease, M- males, F- females, SD- standard deviation, ERD- erosive esophagitis, NERD- nonerosive reflux disease, DE- dental erosion, AC- angular cheilitis, C-Candidiasis, Gi- gingivitis, Gl- glossitis, L- leucoplakia, OSF- oral submucous fibrosis, U- ulceration, P-periodontitis, PE- palate erythema, X- xerostomia, OABS- oral/acid burning sensation, SH- subjective halitosis, NA- not applicable, DE- dental erosions
**Bold- studies included in the meta-analysis*

Narrative synthesis. The descriptive characteristics of the included studies are presented in Table 3. One study was case-control [20], and 9 were cross-sectional reports. The included studies were published between 2003 and 2019. All studies used UGE (upper gastrointestinal endoscopy) for the confirmation of GERD. Six (60%) studies also used pH monitoring [15,16,19–22], with further 2 (20%) including esophageal manometry [15,21] in the diagnosis. One study reported the use of a gastrointestinal fiberscope [13].

Table 3. Measurement characteristics

No.	Lesion/Complaint	Measurement
Lesion		
1.	angular cheilitis (AC)	WHO screening protocol (Warsi 2019),
2.	candidiasis (C)	WHO screening protocol (Warsi 2019),
3.	gingivitis (Gi)	WHO screening protocol (Warsi 2019), PMA index (Watanabe 2017, Yoshikawa 2012), gingival hemorrhage index 0/1/2/3 – Munoz 2003, length of gingival recessions 0/1/2 – Munoz 2003
4.	glossitis (Gl)	WHO screening protocol (Warsi 2019), clinical examination (Watanabe 2017), clinical examination 0/1/2 (Deppe 2015, Yoshikawa 2012)
5.	leucoplakia (L)	WHO screening protocol (Warsi 2019),

6.	palate erythema (PE)	clinical examination (Watanabe 2017), clinical examination (Deppe 2015 0/1/2, Di Fede 2008)
7.	periodontitis (P)	LDH and Hb concentrations in saliva (Adachi 2016), CAL – clinical attachment loss WHO probe (mm) (Deppe 2015)
8.	oral submucous (OSF) fibrosis	OSF staging index (Warsi 2019),
9.	ulceration (U)	WHO screening protocol (Warsi 2019), clinical Examination (Yoshikawa 2012)
Complaint		
10.	oral/acid burning sensation (OABS)	interview (Watanabe 2017, Yoshikawa 2012, Di Fede 2008, Campisi 2008, Corrêa 2008),
11.	subjective halitosis (SH)	interview (Watanabe 2017, Yoshikawa 2012, Di Fede 2008),
12.	xerostomia (X)	WHO screening protocol (Warsi 2019), Saxon test – salivary flow volume (g/2 min) (Watanabe 2017, Yoshikawa 2012), interview (Watanabe 2017, Yoshikawa 2012, Di Fede 2008, Campisi 2008 – standardized questions, Corrêa 2008), stimulated salivary flow (ml/min) (Corrêa 2012, Campisi 2008)

WHO- World Health Organization, PMA- papillary marginal attachment index, LDH- lactate dehydrogenase, Hb- hemoglobin, OSF- oral submucous fibrosis

Table 4. Quantitative analysis comparing non-dental oral cavity lesions in GERD patients versus healthy controls

Lesion/Complaint	No. of studies	Controls	GERD patients	Effect Size Metric (SMD / OR)	P value	I^2 (P value)	Publication bias (P value)
Lesion							
Gingivitis PMA index (SMD, 95% CI)	2	80	145	0.33 (-0.50 to 1.17)	0.43	87.6% (p=0.005)	-
Complaint							
OASB Interview (OR, 95% CI)	5	328	515	6.66 (2.66 to 16.67)	<0.001	65.2% (p=0.02)	0.03
Subjective halitosis (OR, 95% CI)	3	180	345	3.61 (1.01 to 12.92)	0.048	32.0% (p=0.23)	0.27
Xerostomia Saxon test (SMD, 95% CI)	4	208	295	-0.57 (-1.06 to -0.08)	0.02	84.2% (p<0.001)	0.89
Xerostomia Interview (OR, 95% CI)	2	198	320	3.29 (2.26 to 4.80)	<0.001	0.00% (p=0.92)	-

PMA- papillary marginal attachment index, GERD- gastroesophageal reflux disease, SMD- standardized mean difference, OR- odds ratio, CI- confidence interval, OABS- oral acid burning sensation

Lesions. The most frequently reported oral lesions were gingivitis [12,13,17,22] and glossitis [12,13,17,19], followed by palatal erythema [13,19,20]. Two studies reported periodontitis [18,19] and another two oral ulcerations [12,17]. The reported prevalence of gingivitis in GERD patients ranged from 50.8 to 67.4% [21,22], while glossitis was reported in 5.6-7.6% of the cases [13,19]. One study reported a prevalence of 52.1% for periodontitis in GERD patients [19], while 14-21.5% of GERD patients presented palate erythema [19,20].

Complaints. The most reported prevalent complaint was xerostomia [12,13,15–17,19,21], followed by oral acid burning sensation [12,13,16,20,21] and subjective halitosis [12,13,20]. The reported prevalence of xerostomia in GERD patients ranged from 45.7 to 57.5% [12,13,16,20]. The oral acid burning sensation was present in 17.5-52% of GERD patients [12,13,16,20,21], while subjective halitosis was reported in 7.5-49.2% of the cases [12,13,20].

Quantitative synthesis. A total of 1,694 subjects were included, with 687 in the control group and 1,507 patients with GERD. A meta-analysis was performed separately for each type of lesion/complaint and each analysis included 2 to 5 articles, depending on the reporting data (Table 4).

Gingivitis. Two studies, which reported gingivitis as PMA index, were eligible for the meta-analysis12,13. The cumulative analysis (SMD = 0.33, 95% CI: -0.50 to 1.17, p = 0.43) revealed a small, non-significant difference between patients with GERD and controls (Table 4, Figure 2).

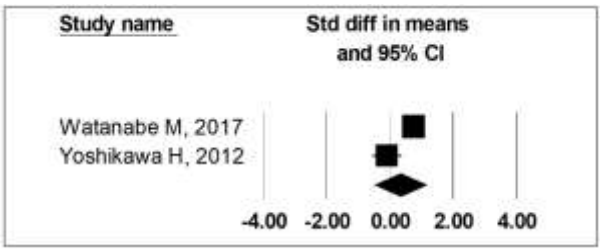

Figure 2. Forest plot summarizing PMA index in GERD patients versus controls

PMA- papillary marginal attachment index, GERD- gastroesophageal reflux disease, CI- confidence interval

Oral acid burning sensation. Five studies, which reported oral acid burning sensation were analyzed quantitatively [12,13,16,20,21]. Patients with GERD had a high cumulative OR (6.66, 95% CI: 2.66 to 16.67, p < 0.001) of experiencing acid burning sensation compared to controls (Table 4, Figure 3).

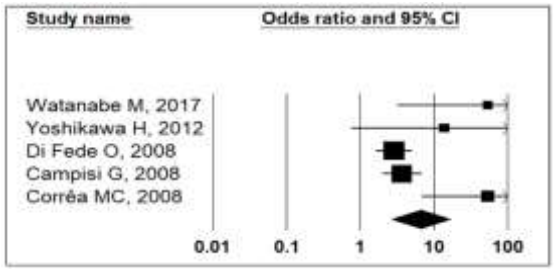

Figure 3. Forest plot summarizing OABS in GERD patients versus controls. *OABS- oral acid burning sensation, GERD- gastroesophageal reflux disease, CI- confidence interval*

Despite the large effect size, a moderate heterogeneity (I2= 65.2%, p = 0.02) and a significant publication bias (p = 0.03) indicate a significant difference in the evidence (Figure 4).

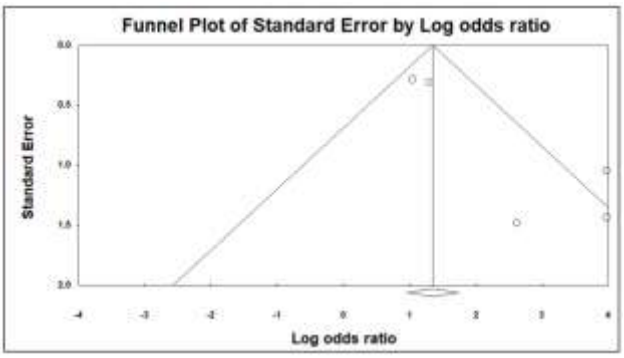

Figure 4. Funnel plot summarizing publication bias of studies which reported OABS in GERD patients versus controls

OABS- oral acid burning sensation, GERD- gastroesophageal reflux disease

Subjective halitosis was reported and quantitatively analyzed in three studies [12,13,20]. GERD was associated with a moderate cumulative OR (3.61, 95% CI: 1.01 to 12.92, p = 0.048) of experiencing halitosis compared to controls (Table 4, Figure 5).

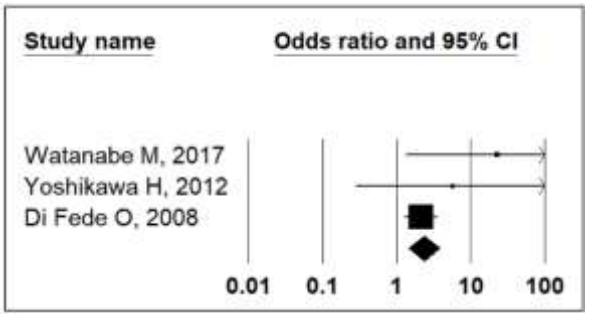

Figure 5. Forest plot summarizing reported subjective halitosis in GERD patients versus controls

GERD- gastroesophageal reflux disease, CI- confidence interval

The results were robust with low heterogeneity (I2= 32%, p = 0.23) and acceptable publication bias (p = 0.27) (Figure 6).

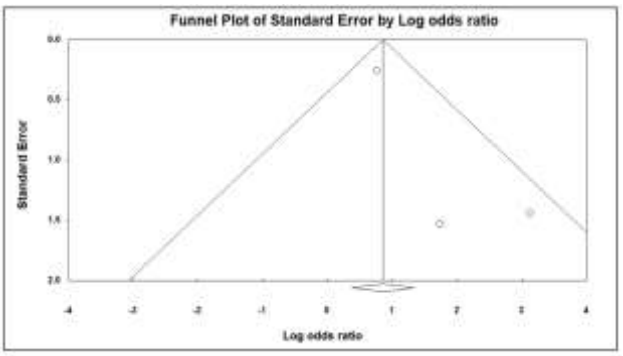

Figure 6. Funnel plot summarizing publication bias of studies which reported subjective halitosis in GERD patients versus controls

GERD- gastroesophageal reflux disease

Xerostomia was reported by assessing the stimulated salivary function in four studies [12,13,15,16] and by interview, reporting the OR in two studies [16,20]. The SMD for the studies reporting the Saxon test score was moderately decreased in patients with GERD (SMD = -0.57, 95% CI: -1.06 to -0.08, p = 0.02) compared to controls (Table 4, Figure 7).

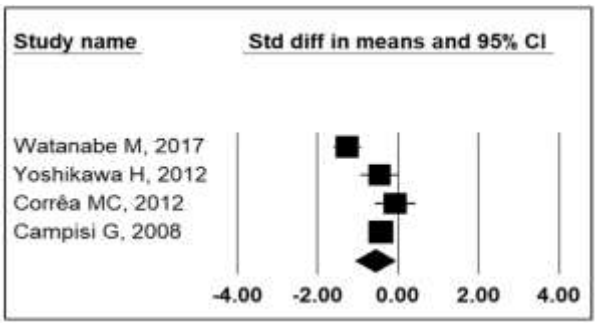

Figure 7. Forest plot summarizing the Saxon test in GERD patients versus controls

GERD- gastroesophageal reflux disease, CI- confidence interval

The studies showed significant heterogeneity (I2 =84.2%, p < 0.001) and acceptable publication bias (p = 0.89) (Figure 8).

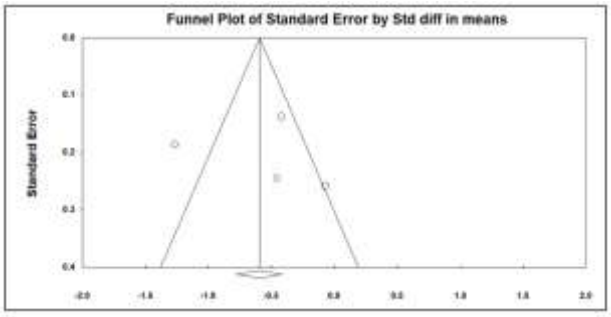

Figure 8. Funnel plot summarizing publication bias of studies which reported the Saxon test in GERD patients versus controls

GERD- gastroesophageal reflux disease

Meanwhile, the analysis of the two studies reporting OR showed a moderately increased risk (OR = 3.29, 95% CI: 2.26 to 4.80, p < 0.001) in patients with GERD versus controls, with low heterogeneity (p = 0.92) (Table 4, Figure 9).

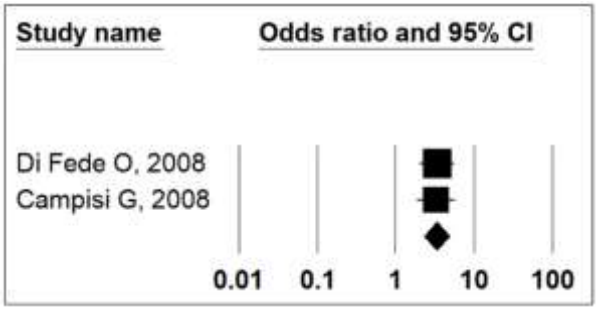

Figure 9. Forest plot summarizing reported xerostomia in GERD patients versus controls

OABS- oral acid burning sensation, GERD- gastroesophageal reflux disease, CI- confidence interval

This systematic review with meta-analysis indicates that individuals diagnosed with GERD are at an increased risk of presenting oral acid burning sensation, subjective halitosis or xerostomia compared to controls without GERD. Non-dental oral cavity lesions such as angular cheilitis, candidiasis, gingivitis, glossitis, leucoplakia, palate erythema, periodontitis, oral submucous fibrosis and ulceration may stand as extraesophageal manifestations of GERD. This review highlights the novel fact that non-dental oral cavity lesions are more frequent in patients diagnosed with GERD than in non-GERD controls. The risk of developing oral lesions such as dental erosions in these patients has been repeatedly investigated and numerous data supporting this association are available [23–27], but the association with non-dental oral cavity lesions/complaints is still insufficiently investigated and controversial.

The biologically possible explanation for the presence of non-dental oral cavity lesions in patients with GERD could stand in the repeated exposure to gastric acid or acidic vapors over a prolonged period of time [25]. Patients with GERD present a reduced tone of the lower esophageal sphincter, which potentates the backflow of the gastric content up to the mouth and airways [28]. Esophagitis stands as the most common complication of GERD, the condition being diagnosed and staged by means of upper digestive endoscopy [3]. Other complications are represented by Barret's esophagus and adenocarcinoma [29]. Currently, an endoscopic examination is not routinely recommended for patients with oral lesions such as dental erosions due to its high cost and patient discomfort [30]. To our knowledge, a standardized oral examination has not yet been defined for GERD patients. Moreover, injured oral mucosa negatively impacts the quality of life, especially functional limitation, physical inability and psychological disabilities and could lead to social isolation [31].

The strengths of this systematic review are represented by the rigorous methodology that was applied for the study selection and data extraction following the PRISMA guidelines. A meta-analysis was conducted for the occurrence of gingivitis diagnosed by means of the PMA index, oral acid burning sensation, subjective halitosis and xerostomia, estimating the odds of developing these conditions in GERD patients. In all 10 included studies, the oral cavity assessment was performed by trained dentists and GERD was diagnosed by experienced gastroenterologists.

The limitations of the study include an important heterogeneity of methods for reporting non-dental oral cavity lesions and complaints, which prevented the quantitative analysis of some studies. Due to the small number of studies which met the inclusion criteria, those reporting ongoing IPP were not excluded. In some cases,

subgroups were merged to form a single group to enable the comparative analysis. In some cases, the calculation of the publication bias was not possible. The majority of the studies included in the meta-analysis had high levels of heterogeneity, suggesting that the results should be interpreted with caution. Even though some studies reported data for NERD versus ERD patients, it could not be used to generate conclusive results. The studies included in the review had a cross-sectional or case report design which could not present the temporal association between GERD and non-dental oral cavity lesions. Finally, this review was limited to English publications, therefore it is possible to have missed relevant publications on the topic.

This study highlights the need for the dental referral of patients diagnosed with GERD. We suggest that a standardized dental clinical examination should be included in the management of these patients. The results of this study indicate the importance of identifying non-dental oral cavity lesions and complaints in the diagnosis of GERD and possibly including a new subtype of GERD associated with oral non-dental manifestations in the Montreal consensus recommendations [32].

Highlights

- ✓ Patients with GERD are at risk of developing oral acid burning sensation, subjective halitosis and xerostomia.
- ✓ Non-dental oral cavity lesions such as angular cheilitis, candidiasis, gingivitis, glossitis, leucoplakia, palate erythema, periodontitis, oral submucous fibrosis and ulceration could represent extraesophageal manifestations of GERD.

Conclusions

The results of this systematic review with meta-analysis indicate that patients with GERD are at high risk of developing oral acid burning sensation, subjective halitosis and xerostomia compared to non-GERD controls. Non-dental oral cavity lesions such as angular cheilitis, candidiasis, gingivitis, glossitis, leucoplakia, palate erythema, periodontitis, oral submucous fibrosis and ulceration could represent extraesophageal manifestations of GERD.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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