

BMJ Open Risk factors associated with oral manifestations and oral health impact of gastro-oesophageal reflux disease: a multicentre, cross-sectional study in Pakistan

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ABSTRACT

Objective Gastro-oesophageal reflux disease (GORD) is a relatively common disorder and manifests with extraoesophageal symptoms, such as dental erosions (DE), cough, laryngitis, asthma, and oral soft- and hard-tissue pathologies. This study aimed (1) to identify oral soft and hard-tissue changes in patients with GORD and (2) to evaluate these oral changes as indices for assessing GORD and its severity.

Setting This cross-sectional study was conducted at four major tertiary care government hospitals, in two metropolitan cities of Pakistan.

Participants In total, 187 of 700 patients who underwent oesophago-gastro-duodenoscopy and having GORD were included in the study. Patients with GORD were divided according to the presence of DE into group A (with DE, chronic/severe GORD) and group B (without DE, mild GORD). Patients who were unconscious and had extremely limited mouth opening were excluded.

Primary and secondary outcome measures Abnormal conditions and lesions of the oral mucosa were recorded. The impact of oral hard and soft-tissue changes on the oral health-related quality of life was assessed using the Pakistani (Urdu) version of the validated Oral Health Impact Profile-14 (OHIP-14) instrument.

Results Oral submucous fibrosis (66.3%), ulceration (59.4%) and xerostomia (47.6%) were significantly more common in group A ($p<0.05$). The prevalence of GORD was 26.7%, within which the prevalence of DE was 35.3%. Unhealthy dietary pattern, nausea/vomiting, oesophagitis, xerostomia, ulceration, gingivitis and angular cheilitis showed a statistically significant association with chronic GORD and DE. All subscales of OHIP-14 were positively correlated ($p<0.05$) in patients with GORD and DE, with notable impact on psychological discomfort ($rs=0.30$), physical disability ($rs=0.29$), psychological disability ($rs=0.27$) and functional limitation ($rs=0.20$).

Conclusion Patients with GORD and DE presented with more severe oral manifestations than did those with GORD and no DE. We recommend timely dental check-ups to assess the severity of both systemic and oral disease.

Strengths and limitations of this study

- This study is the first of its kind to bridge the gap created by either lacking evidence or controversial literature on the effect of gastro-oesophageal reflux disorder (GORD) on oral soft-tissues.
- This study assessed oral health-related quality of life using Oral Health Impact Profile-14 instrument, the results of which highlight how oral health and systemic health are interlinked from a psychological and general well-being perspective.
- General practitioners and gastroenterologists are often the primary healthcare providers for patients with GORD, but while addressing their main gastroenterological concerns, the oral manifestations of these systemic conditions are often overlooked. This study highlights the need for dental referral in patients with upper gastrointestinal disorders (in this case GORD), which can have a marked effect on both systemic and oral health.
- Cross-sectional design of this study limits the ability to rule out confounders and establish causal-inference relationships. Hence, the study results are limited to correlation extent only. We recommend future researchers to assess the reported risk factors in a prospective study design, in order to understand the evolution of oral morbidities linked with the pathogenesis of GORD.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a common disorder, affecting approximately 10%–20% of the general population.¹ The Montreal consensus classifies GORD as an entity manifesting as oesophageal and extraoesophageal symptoms.² The oesophageal symptomatology includes regurgitation or burning retrosternal chest pain, reflux oesophagitis, strictures, Barrett's oesophagus and adenocarcinoma, and the extraoesophageal symptomatology comprises reflux,

cough, laryngitis, asthma and dental erosions (DE).² DE is a multifactorial phenomenon whereby the protective buffering capacity of the oral cavity is compromised by reduced secretion of saliva or high volumes of harmful gastric reflux.³ DE appears to be the most common injury caused by GORD.⁴ The global prevalence of DE in the general population is not accurately known; it varies depending on the underlying cause, and prevalence rates in the range of 2%–77% have been reported.⁵ Tooth involvement seems to be universal, but the most commonly observed damage occurs on the palatal surfaces of the posterior teeth, with a reported prevalence of up to 42%.⁶ Studies have highlighted the detrimental effects of gastroduodenal contents on oral soft-tissue pathology as well as their propensity to cause DE.^{3,7} These include effects on the oesophageal epithelium, soft palate and oral mucosa, and manifest as burning mouth syndrome, aphthoid lesions, hoarseness of voice, erythema of the soft palate and uvula, glossitis, epithelial atrophy and xerostomia.^{6–11} Epithelial atrophy and xerostomia further aggravate GORD-induced injury to the epithelium in the oral cavity and oesophagus.^{12,13}

The severity of DE is directly proportional to the amount of time that gastric acid is in contact with the enamel, so the frequency and duration of the reflux problem can be assessed by the amount of enamel loss and vice versa.^{11,14,15} We hypothesised a strong association between DE and chronic severe GORD, and that an absence of DE would indicate a less severe form of GORD that is of shorter duration. The aims of this study were as follows: to assess the frequency of GORD with and without DE and oral symptoms in patients undergoing oesophago-gastroduodenoscopy (OGD); to determine the association between the severity of GORD and the likelihood of orodental manifestations; and to determine the effect of GORD on oral health-related quality of life (OHRQoL).

MATERIALS AND METHODS

This cross-sectional study was conducted at four major tertiary care government hospitals in two of the major metropolitan cities of Pakistan, namely the twin city of Rawalpindi-Islamabad (Pakistan Institute of Medical Sciences, PIMS and Holy Family Hospital) and Karachi (Jinnah Hospital and Civil Hospital). In total, 187 of 700 patients who underwent OGD along with a comprehensive gastrointestinal (GI) examination over 4 months were diagnosed to have GORD,¹⁶ and confirmed medically by treatment with a proton pump inhibitor were included in the study (100% participation rate). A mandatory dental examination was included to evaluate the orodental effects of GORD. Patients who were unconscious and those with minimal mouth opening (precluding an oral examination) were excluded.

Assessment of demographic and clinical characteristics

A questionnaire was used to collect data on sociodemographics, past and current medical history (comorbidities),

drug history (including use of non-steroidal anti-inflammatory drugs [NSAIDs]), and risk factors for GORD (dietary pattern, addiction profile, consumption of tea, eating habits, weight changes and other GI disorders).

Assessment of OHRQoL

The Oral Health Impact Profile-14 (OHIP-14) is an instrument designed to assess oral OHRQoL and includes seven subscales. The Pakistani (Urdu) validated version of this instrument¹⁶ was used to evaluate factors related to GORD and their effect on the oral cavity concerning speech production, mastication, psychosocial well-being and life in general, and to estimate the impact of GORD on oral and systemic health.

GI examination

All study patients underwent a comprehensive GI examination with baseline laboratory investigations, and were on their routine medical prescriptions.^{15,16} In this study, GORD was diagnosed on the basis of the clinical picture and endoscopic (OGD) findings by a gastroenterologist. The OGD findings in patients with GORD include oesophageal erosions, erythema and strictures, a lax oesophageal sphincter, oesophagitis, Barrett's oesophagus, oesophageal adenocarcinoma and hiatal hernia.¹⁷ Accurate diagnosis of oesophagitis was crucial in this study because it is a risk factor for DE.¹⁰ Compelling evidence from plasma biomarkers (increased Erythrocyte sedimentation rate (ESR)), clinical symptoms (painful swallowing and dysphagia), signs of erythema, inflammation and ulceration on OGD were markers considered for a definitive diagnosis of oesophagitis.¹⁸

Dental examination

WHO criteria for an oral and dental examination was adapted to examine patients for decayed teeth by using the decayed, missed filled teeth (DMFT) index value, mouth opening status and presence of oral submucous fibrosis (OSF) using the OSF staging index.¹⁹ DMFT was recorded as a simple count of decayed and lost teeth. Abnormal conditions and lesions of the oral mucosa (xerostomia, ulceration, candidiasis, gingivitis, angular cheilitis, atrophic glossitis and leukoplakia) were recorded as per WHO screening protocol.^{16,19,20} DE was diagnosed when a patient had tooth hypersensitivity, with accompanying clinical signs of tooth discolouration, dentin exposure, loss of occlusal surfaces and a decrease in tooth height (measured from the cemento-enamel junction to the crest of the enamel).^{19,21,22} All oral examinations were performed by the same dentist (IW).

Statistical analysis

Data analysis was performed using SPSS V.21 (IBM). Categorical variables are reported as frequencies and percentages. Associations between GI symptoms and oral manifestations of GORD were determined using the χ^2 test and logistic regression analysis. The Spearman's rank correlation and Mann-Whitney U test were used to test for associations and difference of the mean

Table 1 Demographic variables and baseline characteristics in patients with GORD

S. no	Demographic variables	N (%)*
1	Gender	
	Male	109 (58.3)
	Female	78 (41.7)
2	Age category	
	<19 years	09 (4.8)
	20–30 years	34 (18.2)
	31–40 years	26 (13.9)
	41–50 years	48 (25.7)
	51–60 years	42 (22.5)
	61–70 years	19 (10.2)
	71–80 years	09 (4.8)
3	Race/ethnicity	
	Sindhi	15 (8.0)
	Balochi	05 (2.7)
	Punjabi	102 (54.5)
	Pathan	28 (15)
	Kashmiri	06 (3.2)
	Urdu Speaking Mohajirs	31 (16.6)
4	Domicile	
	Urban	119 (63.6)
	Rural	68 (36.4)
5	Socioeconomic status (SES)†	
	Low	116 (62)
	Moderate	66 (35.3)
	High	05 (2.7)
6	Dietary pattern‡	
	Healthy diet	23 (12.3)
	Satisfactory diet	80 (42.8)
	Unhealthy diet	84 (44.9)
7	Addiction	
	Smoking	50 (26.7)
	Oral tobacco	57 (30.5)
	Alcohol	05 (2.7)
8	Tea consumption	
	Yes	136 (72.7)
	No	51 (27.3)
9	NSAIDs consumption	
	Yes	86 (46.0)
	No	101 (54.0)
10	History of body ache/general body pain	
	Yes	83 (44.0)
	No	104 (56.0)
11	Weight loss (from <5 kg to >20 kg)	
	No	45 (24.1)

Continued

Table 1 Continued

S. no	Demographic variables	N (%)*
	1–5 kg	72 (38.5)
	5–10 kg	13 (7.0)
	10–15 kg	36 (19.3)
	15–20 kg	15 (8.0)
	>20 kg	06 (3.2)
12	Comorbidities	
	Hypertension	65 (34.8)
	Diabetes mellitus	43 (23)
	Hepatitis B	08 (4.3)
	Hepatitis C	64 (34.2)
	Chronic liver disease	35 (18.7)
13	Dental erosions (DE)	
	Group A: GORD with DE	66 (35.3)
	Group B: GORD without DE	121 (64.7)
14	GORD (alone) and (in combination with other GI illness)	
	GORD alone	106 (56.7)
	GORD with additional upper-GI conditions	81 (43.3)
	i. Gastritis	16 (19.8)
	ii. Portal gastropathy	09 (11.2)
	iii. Peptic ulcer disease	08 (10.2)
	iv. GORD oesophagitis	04 (4.8)
	v. Hiatal hernia	04 (4.3)
	vi. Others	40 (49.7)

*Items in bold highlight notable prevalence in each category.

†SES (categorised on the basis of monthly family income, number of family dependents and educational status).

 ‡Dietary pattern (healthy diet refers to a balanced diet; satisfactory diet: being intermediary between healthy and unhealthy diet, explicitly relating to occasionally eating junk food, while diet relatively lacks in natural abrasives like fruits/vegetables, cereals, leafy vegetables and fibres; unhealthy diet refers to consuming high fatty/oily meals, frequent consumption of junk food/fast food and soft drinks, while completely devoid of natural abrasives).¹⁶

GI, gastrointestinal; GORD, gastro-oesophageal reflux disease; NSAIDs, non-steroidal anti-inflammatory drugs.

values between GORD groups and OHIP-14 subscales, respectively. A binary outcome variable (GORD without DE, 0; and GORD with DE, 1) was created to compute results. This paper presents multiple regression models to report risk factors related to the outcome variable (GORD with DE). The results are reported as crude odds ratio (CORs), adjusted odds ratio (AOR), with 95% confidence interval (CI) and p values. Bivariate logistic regression was used to obtain COR's for assessing the 'likelihood of GORD and DE' against 'independent predictor variables', extracted from tables 1, 2 and 4. Variables with $p \leq 0.2$ were entered in the multivariable logistic regression model to obtain AOR's. Model's performance was

evaluated using measures of discrimination. It addresses the extent to which the model predicts a higher probability of the outcome (GORD with DE), with certain set of predictors in a model; using the area under the receiver operating characteristic curve (AU-ROC or AUC) or *c*-statistics. AUC value range from 0.5 (no discrimination) to 1 (perfect discrimination).²³

Patient and public involvement

No patients were involved in the development of this study. However, a pilot group of patients played a crucial role in testing the responsiveness of the questionnaire and identifying gaps in the study. Additional study variables, including xerostomia, OSF and DMFT, were added to the clinical dental section after observing consistency of these characteristics in the specified population. Moreover, the translated OHIP-14 questionnaire was tested, and feedback

was obtained from the pilot patients; this process helped in making various amendments concerning language and comprehension of the OHIP scale items.¹⁶ Within the GI section, it was observed from the patient's history that they were prone to self-medication (particularly NSAIDs) due to the history of chronic back pain. Therefore, these variables were also assessed in this study. All the patients were assigned a unique identifier code to maintain patient privacy and confidentiality. The patients did not play any role in the initiation of this study or drafting this manuscript.

While departmental permissions were sought from all four participating hospitals (CHK, JPMC, PIMS and Holy Family), before participant enrolment, written informed consent was obtained from all study participants after explaining the study protocol.

Table 2 Gastrointestinal (GI) signs and symptoms in patients with GORD

GI symptoms	Group A (n _a =66)	Group B (n _b =121)	All (n=187)	OR* (95% CI)	P value
Heartburn/regurgitation					
Yes	63	115	178 (95.2%)	1.096 (0.265 to 4.531)	0.9
No	3	6	09 (4.8%)		
Nausea/vomiting					
Yes	48	107	155 (82.9%)	0.349 (0.160 to 0.759)	0.006†
No	18	14	32 (17.1%)		
Abdominal pain/ discomfort					
Yes	49	92	141 (75.4%)	0.909 (0.455 to 1.815)	0.786
No	17	29	46 (24.5%)		
Abdominal distension					
Yes	40	62	102 (54.5%)	1.464 (0.796 to 2.692)	0.219
No	26	59	85 (45.4%)		
Early satiety/loss of appetite					
Yes	44	62	106 (56.7%)	1.903 (1.020 to 3.551)	0.042†
No	22	59	81 (43.3%)		
Dysphagia					
Yes	32	48	80 (42.8%)	1.431 (0.782 to 2.620)	0.244
No	34	73	107 (57.2%)		
Haematemesis					
Yes	27	44	71 (38.0%)	1.212 (0.655 to 2.240)	0.54
No	39	77	116 (62.0%)		
Melena					
Yes	36	46	82 (43.9%)	1.957 (1.065 to 3.593)	0.029†
No	30	75	105 (56.1%)		

Odds Ratios in bold exhibit corresponding GI symptoms as significantly associated with Chronic GORD. Group A, chronic/severe GORD with DE. Group B, mild GORD without DE.

*OR (of GI symptoms against GORD+DE as reference category).

†P<0.05 (χ^2 test of proportion) was statistically significant.

DE, dental erosions; GORD, gastro-oesophageal reflux disease.

Table 3 Oral manifestations in patients with GORD

Oral manifestations	Group A (n=66)	Group B (n=121)	All (n=187)	COR (95% CI)	P value*	AOR (95% CI)	P value†
1. Xerostomia							
Yes	47	42	89 (47.6%)	4.653 (2.426 to 8.923)	<0.01*	2.372 (1.047 to 5.373)	0.038†
No	19	79	98 (52.4%)	1		1	
2. Ulceration							
Yes	60	51	111 (59.4%)	13.725 (5.506 to 34.218)	<0.01*	6.705 (2.481 to 18.122)	<0.01†
No	6	70	76 (40.6%)	1		1	
3. Gingivitis							
Yes	47	26	73 (39.0%)	9.038 (4.547 to 17.968)	<0.01*	4.768 (2.123 to 10.706)	<0.01†
No	19	95	114 (61.0%)	1		1	
4. Candidiasis							
Yes	20	20	40 (21.4%)	2.196 (1.078 to 4.471)	0.028*	0.706 (0.267 to 1.868)	0.483
No	46	101	147 (78.6%)	1		1	
5. Angular cheilitis							
Yes	24	12	36 (19.3%)	5.190 (2.382 to 11.312)	<0.01*	2.526 (1.038 to 6.148)	0.041†
No	42	109	151 (80.7%)	1			
6. Atrophic glossitis							
Yes	30	27	57 (30.5%)	2.901 (1.520 to 5.538)	0.001*	–	–
No	36	94	130 (69.5%)	1			
7. Leukoplakia							
Yes	2	6	08 (4.3%)	0.599 (0.117 to 3.055)	0.533	–	–
No	64	115	179 (95.7%)	1			
8. Oral submucous fibrosis							
Yes	53	71	124 (66.3%)	2.871 (1.417 to 5.818)	0.003*	–	–
No	13	50	63 (33.7%)	1			
9. DMFT status							
<3	24	64	88 (47.06%)	–	0.069	–	–
3-10	24	37	61 (32.62%)				
>10	18	20	38 (20.32%)				

Items in bold represent major findings (of note) in their respective field.

* $P < 0.05$ (χ^2 test) was considered statistically significant. Group A, chronic/severe GORD with DE. Group B, mild GORD without DE.

DMFT (decayed, missed, filled teeth), pertaining to tooth decay and tooth loss. DMFT <3 (acceptable), DMFT 4–10 (average), DMFT >10 (poor).¹⁶ COR, crude OR (χ^2 /linear regression); AOR, adjusted OR (values from multivariate logistic regression analysis).

†ORs were computed for oral manifestations against a reference variable, 'GORD with DE.' Using backward selection (likelihood ratio) method, variables were entered in the multivariable analysis. The adjustment was made for atrophic glossitis, oral submucous fibrosis, leukoplakia and DMFT status. Area under ROC (AUROC) value: 0.855, was used as an assessment of the multivariable logistic regression model's discriminative ability (to predict between the presence and absence of DE).

DE, dental erosions; GORD, gastro-oesophageal reflux disease; ROC, receiver operating characteristic curve.

RESULTS

Most study participants were males (58.3%), around 80% were in the adult age group (41–60 years), as shown in [table 1](#). The study sample was ethnically and racially diverse; most participants were Punjabis (54.5%), followed by Urdu-speaking Mohajirs (16.6%), Pathans (15%) and Sindhis (8%). Most were urban residents (63.6%) of intermediate (35.3%) to low (62%) socioeconomic status. The addiction profile predominantly consisted of oral tobacco (30.5%) and cigarette smoking (26.7%), with a low rate of alcohol consumption (2.7%). The most commonly consumed beverage was chai tea (72.7%). A sizeable

proportion experienced generalised body pain (44%), and reported self-medication, particularly with NSAIDs (46%). The most common comorbidities were diabetes (34.8%), hypertension (23%), hepatitis C (34.2%) and chronic liver disease (CLD) (18.7%). Slightly more than half (56.7%) of the study population had GORD alone, while the remaining had additional upper GI conditions, including gastritis (19.8%), portal gastropathy (11.2%), peptic ulcer disease (PUD) (10.2%), GORD-related oesophagitis (4.8%) and hiatal hernia (4.3%).

DE is a known comorbidity of chronic GORD; hence, we divided the patients based on the presence of DE

into two groups (binary variable), namely group A (with DE, chronic/severe GORD; $n_a=66$, 35.3%) and group B (without DE, mild GORD; $n_b=121$, 64.7%). The oral and systemic findings were compared between the two groups. **Table 2** shows the GI signs and symptoms that were found in both study groups; the most common of which was heartburn/regurgitation (95%), followed by nausea/vomiting (82%) and dysphagia (42%). A statistically significant difference in the frequency of nausea/vomiting (OR 0.35, 95% CI 0.16 to 0.76, $p=0.006$), early satiety/loss of appetite (OR 1.90, 95% CI 1.02 to 3.55, $p=0.042$) and melena (OR 1.96, 95% CI 1.07 to 3.59, $p=0.029$) was found between patients who had GORD with DE than did those without DE.

The oral manifestations associated with GORD in groups A and B are shown in **table 3**. Overall, patients with GORD and DE had significantly more oral manifestations than did those without DE. There was also a trend of worse dentition status (poor DMFT >10), as indicated by a higher mean DMFT index value in group A than in group B, suggesting that teeth with DE were more vulnerable to decay and tooth loss.

The coexistence of gastro-oesophageal reflux disease (GORD) and DE was found most likely (in decreasing order of frequency) with aphthoid ulcerative lesions (OR 13.7, $p<0.01$), followed by gingivitis (OR 9.0, $p<0.01$), angular cheilitis (OR 5.2, $p<0.01$), xerostomia (OR 4.7, $p<0.01$), atrophic glossitis (OR 2.9, $p=0.001$), OSF (OR 2.9, $p=0.003$) and oral candidiasis (OR 2.2, $p=0.028$). Oral manifestations with a $p<0.05$ were included in the multivariable logistic regression model, hence leukoplakia and DMFT were excluded. This multivariable logistic regression model was created by the backward selection (likelihood ratio) method. Given that candidiasis has a biological association with GORD and DE, it was retained in the model. Interestingly, the multivariable logistic regression model had a good AUROC, with a value of 0.855. The highest correlation for GORD with DE was found with ulceration (AOR 6.71, 95% CI 2.48 to 18.12, $p<0.01$) and gingivitis (AOR 4.76, 95% CI 2.12 to

10.71, $p<0.01$), followed by angular cheilitis (AOR 2.53, 95% CI 1.03 to 6.15, $p=0.041$) and xerostomia (AOR 2.37, 95% CI 1.05 to 5.37, $p=0.038$). However, candidiasis did not retain its significance in the multivariable analysis.

Table 4 shows the seven-subscale (OHIP-14) scores for groups A and B. The mean values for all subscales were relatively higher in group A, suggesting a higher risk of 'poor OHRQoL,' than that in group B. Spearman rank correlation (rs) and Mann-Whitney U statistical tests are used for correlations, and to compare means, in both groups A and B, respectively. Mann-Whitney U test reveals that a statistically significant difference has been observed for all OHIP subscales (except social disability) when compared between the two groups (A and B). The coexistence of GORD and DE had a positive correlation with OHIP subscales ($p<0.05$), with notable impact on psychological discomfort (rs=0.30), physical disability (rs=0.29), psychological disability (rs=0.27) and functional limitation (rs=0.20).

Table 5 shows the bivariate relationship between the significant study variables (extracted from **tables 1, 2 and 4**), and the dichotomous/binary outcome variable (ie, GORD with DE, as the reference category), computed in a logistic regression model. Univariate analysis revealed that patients with an unhealthy diet were more likely to develop GORD with DE than those with a healthy diet (OR 6.03, 95% CI 1.89 to 9.27). Early satiety/loss of appetite (OR 1.90, 95% CI 1.020 to 3.56) and nausea/vomiting (OR 0.35, 95% CI 0.16 to 0.76) increased the likelihood of developing DE by 1.90-fold and 0.35-fold, respectively. Moreover, melena was found to be a common manifestation in this population with chronic GORD (OR 1.96, 95% CI 1.07 to 3.59). Patients with PUD were more likely to develop chronic GORD with DE (OR 2.83, 95% CI 1.08 to 7.42). Similarly, the OHIP subscale scores for functional limitation, physical pain, physical disability, psychological discomfort and psychological disability were sensitive to the severity of GORD and the presence of DE.

The results of the multivariable logistic regression model are also presented in **table 5**, with adjustments made for all independent variables. Some variables that

Table 4 Psychometric properties of OHIP-14, correlated with GORD, with and without DE

OHIP-14 subscales characteristics	Mean subscale (SD)		Statistical tests	
	With DE (group A) $n_a=66$	Without DE (group B) $n_b=121$	Spearman rank: rs correlation value	Mann-Whitney U test (p value)*
Functional limitation	3.530 (2.199)	2.5702 (1.92712)	0.200*	3065.0 (0.006)*
Physical pain	1.182 (1.264)	0.7273 (0.96609)	0.167*	3260.0 (0.023)*
Psychological discomfort	5.167 (1.853)	4.0744 (1.98396)	0.297*	2625.0 (<0.001)*
Physical disability	6.394 (2.745)	4.4463 (2.81351)	0.288*	2672.0 (<0.001)*
Psychological disability	4.591 (1.745)	3.5868 (1.94795)	0.271*	2754.5 (<0.001)*
Social disability	7.106 (2.835)	6.1405 (3.42127)	0.142	3332.5 (0.053)
Handicap	1.682 (1.230)	1.2149 (1.31153)	0.193*	3099.0 (0.008)*

Bold highlight represents important values in each statistical test results.

*Correlation is significant at $p<0.05$ level (two tailed).

DE, dental erosions; GORD, gastro-oesophageal reflux disease; OHIP-14, Oral Health Impact Profile-14; rs, ranks correlation coefficient.

Table 5 Risk factors associated with GORD and dental erosions: results of the univariate and multivariable analysis

Characteristics	GORD with dental erosions			
	COR (95% CI)	P value	AOR (95% CI)	P value
1. Dietary pattern		<0.01*		<0.001*
Healthy	1		1	
Satisfactory	1.096 (0.325 to 3.697)		0.234 (0.041 to 1.320)	
Unhealthy	6.034 (1.889 to 19.268)		2.307 (0.403 to 13.207)	
2. GI symptom: nausea/vomiting		0.008*		0.004*
No	1		1	
Yes	0.349 (0.160 to 0.759)		0.130 (0.033 to 0.512)	
3. GI symptom: early satiety/loss of appetite		0.043*		0.262
No	1		1	
Yes	1.903 (1.020 to 3.551)		1.778 (0.650 to 4.867)	
4. GI symptom: melena		0.030*		0.421
No	1		1	
Yes	1.957 (1.065 to 3.593)		1.509 (0.554 to 4.111)	
5. GI disorder: oesophagitis		0.20		0.014*
No	1		1	
Yes	2.398 (0.621 to 9.255)		12.427 (1.658 to 93.143)	
6. GI disorder: peptic ulcer disease		0.035*		0.302
No	1		1	
Yes	2.825 (1.075 to 7.423)		2.143 (0.505 to 9.095)	
7. GI disorder: hiatal hernia		0.20		0.201
No	1		1	
Yes	0.251 (0.03 to 2.082)		0.159 (0.010 to 2.655)	
8. GI disorder: portal gastropathy		0.214		-
No	1		-	
Yes	1.786 (0.715 to 4.458)		-	
9. GI disorder: gastritis		0.06		0.065
No	1		1	
Yes	2.013 (0.970 to 4.179)		3.388 (0.926 to 12.398)	
10. OHIP subscale 1: functional limitation		0.047*		0.277
1=Null	1		1	
2=Mild	1.379 (0.506 to 3.753)		0.511 (0.106 to 2.464)	
3=Moderate	1.495 (0.581 to 3.843)		0.537 (0.132 to 2.193)	
4=Severe	3.646 (1.204 to 11.044)		0.607 (0.086 to 4.313)	
5=Advanced	5.469 (1.265 to 23.640)		6.149 (0.491 to 76.934)	
11. OHIP subscale 2: physical pain		0.023*		0.118
1=Null	1		1	
2=Mild	0.484 (0.168 to 1.391)		0.202 (0.034 to 1.186)	
3=Moderate	1.935 (0.929 to 4.032)		2.706 (0.633 to 11.574)	
4=Severe	3.116 (0.917 to 10.591)		4.271 (0.473 to 38.585)	
5=Advanced	6.677 (0.668 to 66.769)		2.391 (0.104 to 55.127)	
12. OHIP subscale 3: physical disability		0.002*		0.024*
1=Null	1		1	
2=Mild	0.346 (0.057 to 2.095)		0.042 (0.003 to 0.674)	
3=Moderate	3.033 (0.936 to 9.822)		0.861 (0.101 to 7.331)	

Continued

Table 5 Continued

Characteristics	GORD with dental erosions			
	COR (95% CI)	P value	AOR (95% CI)	P value
4=Severe	3.414 (1.011 to 11.527)		0.125 (0.010 to 1.613)	
5=Advanced	15.750 (2.335 to 106.227)		0.564 (0.020 to 16.163)	
13. OHIP subscale 4: psychological discomfort		0.002*		0.358
1=Null	1		1	
2=Mild	2.857 (0.282 to 28.960)		2.105 (0.073 to 60.804)	
3=Moderate	2.264 (0.262 to 19.563)		3.080 (0.144 to 65.939)	
4=Severe	6.303 (0.741 to 53.650)		3.303 (0.145 to 75.217)	
5=Advanced	11.692 (1.302 to 105.028)		10.356 (0.457 to 234.689)	
14. OHIP subscale 5: handicap		0.057		0.171
1=Null	1		1	
2=Mild	1.981 (0.795 to 4.935)		1.884 (0.415 to 8.563)	
3=Moderate	2.869 (1.303 to 6.315)		2.257 (0.569 to 8.948)	
4=Severe	3.900 (1.282 to 11.860)		9.210 (1.348 to 62.911)	
5=Advanced	1.891 (0.600 to 5.964)		0.756 (0.126 to 4.529)	
15. OHIP subscale 6: psychological disability		0.006*		0.207
1=Null	1		1	
2=Mild	3.000 (0.520 to 17.316)		13.130 (0.913 to 188.820)	
3=Moderate	2.763 (0.582 to 13.122)		6.336 (0.638 to 62.938)	
4=Severe	8.077 (1.682 to 38.784)		13.513 (1.273 to 143.448)	
5=Advanced	8.437 (1.457 to 48.851)		9.434 (0.899 to 98.955)	

Odds Ratios and their respective p-values in bold exhibit corresponding risk factors as significantly associated with Chronic GORD (ie, GORD with DE).

All study variables expressing $p < 0.2$ in univariate analysis were included in the multivariable analysis and are presented here in this table.

* $P < 0.05$ was considered statistically significant (bold highlight). COR, crude/unadjusted ORs (obtained from univariate analysis); AOR, adjusted ORs for all independent variables (obtained from multivariable analysis, by stepwise selection method).

GI, gastrointestinal; GORD, gastro-oesophageal reflux disease; OHIP, Oral Health Impact Profile-14.

had a statistically significant association with DE in the univariate analysis (ie, loss of appetite, melena, PUD and the OHIP subscales: functional limitation, physical pain, psychological discomfort and psychological disability) were no longer significant in multivariable analysis. Portal gastropathy had a $p > 0.2$, therefore excluded from multivariable analysis. However, an unhealthy diet (AOR 2.31, 95% CI 0.40 to 13.21), nausea/vomiting (AOR 0.13, 95% CI 0.03 to 0.51), oesophagitis (AOR 12.43, 95% CI 1.66 to 93.14) and advanced physical disability (AOR 0.56, 95% CI 0.02 to 16.16) retained their significant association with GORD and DE, in the multivariable analysis.

Using the backward selection (likelihood ratio) method, all 17 variables that were significant in univariate analysis (of tables 3 and 5) were entered in the cumulative multivariable logistic regression model (as shown in table 6). In this model (based on clinical signs and symptoms), gingivitis (AOR 7.516, 95% CI 2.517 to 22.443; $p < 0.001$), ulceration (AOR 6.609, 95% CI 2.007 to 21.765; $p = 0.002$), angular cheilitis (AOR 4.028, 95% CI 1.237 to 13.115; $p = 0.021$), xerostomia (AOR 3.005, 95% CI 1.026 to 8.805; $p = 0.045$), unhealthy diet (AOR 0.474, 95% CI

0.091 to 2.452; $p = 0.003$) and nausea/vomiting (AOR 0.256, 95% CI 0.067 to 0.980; $p = 0.047$) were significant in relation to GORD and DE. The AUROC was used to assess the ability of the multivariable regression model to discriminate between GORD with DE and GORD without DE. The AUROC was 0.922, indicating excellent discrimination and confirming that these variables presented in the model are major clinical risk factors for chronic GORD (ie, GORD with DE).

DISCUSSION

GORD with DE and its associated risk factors has been the subject of much research interest in recent years. The present study focused on patients who had GORD with or without DE and recorded the prevalence, distribution, severity and risk factors of this clinical entity in a relatively large sample. The influences of known risk indicators and other possible determinants that have been less well studied in the past were also investigated.^{7 11}

GORD has multiple systemic effects, particularly in the GI tract (table 2). There is considerable medical

Table 6 Clinical Risk factors for GORD with DE: results of the cumulative multivariable logistic regression model

Risk factors (for GORD with DE's)	COR (95% CI)	P value*	AOR (95% CI)	P value†
1. Unhealthy dietary pattern				
Yes	6.034 (1.889 to 19.268)	<0.01	0.474 (0.091 to 2.452)	0.003
No	1		1	
2. Nausea/vomiting				
Yes	0.349 (0.160 to 0.759)	0.008	0.256 (0.067 to 0.980)	0.047
No	1		1	
3. Xerostomia				
Yes	4.653 (2.426 to 8.923)	<0.01	3.005 (1.026 to 8.805)	0.045
No	1		1	
4. Ulceration				
Yes	13.725 (5.506 to 34.218)	<0.01	6.609 (2.007 to 21.765)	0.002
No	1		1	
5. Gingivitis				
Yes	9.038 (4.547 to 17.968)	<0.01	7.516 (2.517 to 22.443)	<0.01
No	1		1	
6. Angular cheilitis				
Yes	5.190 (2.382 to 11.312)	<0.01	4.028 (1.237 to 13.115)	0.021
No	1		1	

Odds ratios in bold exhibit corresponding clinically significant risk factors, highly associated with Chronic GORD (ie, GORD with DE). CORs (crude ORs) represent a univariate analysis, while AORs (adjusted ORs) represent multivariable analysis (using backward-elimination method).

*All significant variables with $p < 0.05$, obtained through univariate analysis (from tables 3 and 5), are computed against dichotomous outcome variable, 'GORD with DE.'

†Using backward selection (likelihood ratio), all 17 variables were entered in multivariable logistic regression model; only 6 of 17 significant variables (from tables 3 and 5), retained significance within the final regression model, which are shown here in this table. This model was tested for discrimination, with an AUROC value of 0.922.

AUROC, area under the receiver operating characteristic curve; DE, dental erosions; GORD, gastro-oesophageal reflux disease.

literature on GORD and its impact on the oral hard tissue (ie, DE), as well as its periodontal effects⁸; however, data on the relationship between GORD-mediated acidic oral mucosal lesions and oral health are either scarce or controversial.^{7-12 14-16 22-25} Our finding of a prevalence of DE in patients with GORD of 35.3%, fits well within the regionally (South Asian population) reported prevalence of DE (ranges between 5.0% and 58.4%)^{24 26-28}; while global prevalence ranges from 2% to 77%, this wide range differs with age, gender, ethnicity and population-based underlying risk factors.⁵ The influence of notable risk factors (such as obesity, metabolic syndrome, strong addiction pattern and alcohol consumption) for development of GORD and DE, in this specific population, was negligible; which supports the fact that the reported prevalence of DE in this study was relatively low (unlike the western population).^{17 29 30} Moreover, this study's population was predominantly hospital-based patients, seeking tertiary care for chronic ailments. As evident around 43% of subjects have other GI pathologies in addition to GORD, while chronic illness like hepatitis C (34%) and CLD (19%) contribute as eminent comorbidities; Furthermore, around 75% of this population had

experienced weight loss of varying degrees, which eliminates obesity (or weight gain) as a risk factor.

Our results indicate that xerostomia, ulceration, gingivitis and angular cheilitis have the highest correlation with GORD and DE. Some of our findings are in accordance with the few previous studies.^{7 11} Since there have been lacking studies assessing the prevalence of xerostomia and oral lesions in patients with GORD, therefore, literature reveals mixed results.^{4 9 24 31} Saliva is considered to play a leading role in protecting the oesophageal mucosa against gastric reflux, and its qualitative (eg, deficiencies of salivary growth factor and cytokines) and quantitative (eg, hyposalivation) abnormalities have been linked to the pathogenesis of GORD,^{13 32-34} compromised dental health³⁵ and DE.³⁶ The pathogenesis of GORD appears to be connected with the decreased production of saliva, and our findings suggest that xerostomia should be included in the extraoesophageal symptomatology of GORD.^{7 11 37}

Approximately 60% of participants had ulcerative lesions on the soft and hard palate mucosa, buccal mucosa, uvula and tongue, which could not be characterised clinically as any other disease; these lesions are typically recognised as 'soft-tissue aphthoid lesions' related

to GORD,^{47 9 24 31} and are caused directly by the corrosive effects of refluxed acid.

A recent study in a rat model of the soft palate by Habesoglu *et al*⁶ identified epithelial and microscopic alterations in response to acid injury. Interest in this phenomenon dates to the late 1980s, when a study by Järvinen *et al* demonstrated a marked prevalence of oral mucosal changes in the presence of GORD, including a burning mouth, aphthoid lesions, erythema of the soft palate and uvula, glossitis, and epithelial atrophy.⁹ However, these findings were called into question by the studies of Ranjitkar *et al*¹² and Petrucci *et al*²⁵ who found that mucosal changes are quite common and not an entity-specific for GORD. Similarly, Deppe *et al*⁸ also studied the effects of GORD on the oral mucosa and found positive and negative signs for erythema and ulceration, respectively, but could not find a statistically significant difference between their erosive and non-erosive reflux groups. In addition, a study by Meurman *et al*⁵ found no mucosal changes that could be linked to GORD. On the contrary, a recent retrospective analysis by Watanabe *et al* identified significant association of GORD with dysphagia, xerostomia, oral ulceration, gingivitis and oral inflammation on buccal mucosa and tongue.⁷ Considering the findings of Watanabe *et al* and Rajalalitha and Vali,^{7 38} we hypothesised that the chronic acid injury caused by GORD would be a source of persistent irritation and inflammation affecting the oral mucosa, resulting in the infiltration of inflammatory markers. These markers include increased populations of interleukins, cytokines, tumour necrosis factor-alpha, interferon-alpha and growth factors such as transforming growth factor-beta, which are produced at the site of inflammation. This mechanism of inflammation is exaggerated in situations of chronic and constant irritation such as GORD and supraoesophageal reflux disease.^{26 38–41} While this finding is accompanied by epithelial atrophy and fibroelastic changes in the lamina propria.^{38 42} Also, this mechanism is consistent with the significant finding of OSF in our study population, which can lead to metaplastic changes in the oral mucosa and can also cause restricted mouth opening, resulting in trismus, eating difficulties, impaired speech and generalised impairment of oral health.^{7 16 38–40} Our study findings demonstrate a positive association of chronic GORD with OSF, which is an oral precancerous lesion.⁴² OSF has never been reported in association with GORD, partly because these oral pathologies were not studied in-depth among GORD population.^{3–15 20–22 24–28 43 44} However, because of its significant impact on quality of life, it should be considered and addressed in future researches.

With chronic GORD-mediated acid exposure, the salivary gland epithelium sustains severe damage (ie, epithelial metaplasia), resulting in xerostomia.^{7 11 20 26} This association may further aggravate acid-mediated oro-oesophageal epithelium injury, resulting in GORD-related oesophagitis.^{10 13 45} Other conditions, including oral ulceration, associated infections (candidiasis and angular cheilitis) and gustatory dysfunction, are also common.^{7 45}

Corrêa *et al* noted that patients with chronic GORD had reduced salivary buffering capacity and concluded that this was the predominant cause of tooth erosion.⁴⁶ The same study also reported a lower prevalence of dental caries, which was attributed to the low prevalence of cariogenic bacteria (Lactobacilli and Streptococci) in the saliva of patients with chronic GORD. This may have a possible association with GORD mediated DE that needs confirmation in future studies. However, our findings with regard to dental caries are contrary to Corrêa *et al*, in sense that the mean DMFT index values were higher in the group with GORD and DE (DMFT >4 in 63.6%) than in the group with GORD and no DE (DMFT >4 in 47.1%). We postulate that the additive effects of direct acid injury, low salivary buffering capacity and increased opportunistic bacterial populations caused a marked increase in tooth decay and loss (indicated by increased DMFT-index values in our study), as evident in the high-risk population with chronic GORD and DEs.^{7 21 35} However, it can also be attributed to poor oral hygiene status, primarily because 27% of our study population were smokers, and 30% chewed tobacco.⁴⁷ An acidic/unhealthy dietary pattern was common in GORD population,²² as was excessive consumption of traditional beverages (ie, sweet chai/milktea—73%), which would also have contributed to a low oral pH and provided a favourable environment for opportunistic bacteria causing tooth decay and tooth loss.^{7 48 49}

There is a wealth of literature identifying DE as being comorbid with GORD,² and a review by Ranjitkar *et al* reported the median prevalence for DE in patients with GORD to be 24%.²¹ Accordingly, the Montreal consensus postulated that the prevalence of DE is directly related to GORD, particularly when noted on the lingual and palatal tooth surfaces.² Our study findings are consistent with the concept that DE has a significant association with GORD and may serve as a marker of disease severity. As in a study by Meurman *et al*,⁵ our study's statistical comparison of patients with GORD with and without DE demonstrated that unlike subjective oral symptoms, oral manifestations were significantly more common in the group with GORD and DE.

Considering the findings of Meurman *et al*,⁵ we used the validated OHIP-14 instrument,¹⁶ instead of subjective oral symptoms, and perceived oral health to assess the impact of severity of GORD (with DE) on oral health from a psychological and general well-being perspective. Until now, this tool has not been tested among this population.²² Using the OHIP-14, we found that GORD with DE was significantly correlated ($p < 0.05$) with the psychometric characteristics (of OHIP-14) namely: psychological discomfort, physical disability, psychological disability, functional limitation, handicap and physical pain. This result is consistent with our finding that GI conditions and their oral manifestations have a considerable adverse impact on oral health.¹⁶ Notably, in this study, 43.3% of the study population had GORD alone, and the rest had additional upper GI conditions, including gastritis, portal gastropathy, PUD, GORD-related oesophagitis and hiatal hernia, which are believed to be factors

that initiate and/or lead to progression of GORD.^{16 50–52} However, a significant proportion of patients were habitual towards unhealthy dietary pattern (45%), experienced frequent nausea/vomiting (83%) and also self-medicated themselves with NSAIDs for pain relief (46%), which are risk factors that further aggravate upper-GI illness (particularly GORD).^{22 27 50}

This study has some limitations. First, the study design is cross-sectional, limits the ability of the study results to correlation extent only. Since this study is the first of its kind to extensively report risk factors, future prospective cohort studies are needed to establish causality. Second, the staging of DE was not recorded. Third, only one investigation was used to diagnose GORD, and no measures of disease severity, such as manometry, 24-hour pH monitoring or biopsies, were included.⁴⁶ Fourth, other oral manifestations of GORD that might have a causal relationship with DE, such as periodontal and gingival diseases, were not recorded in detail.⁷ Fifth, we did not control for the effect of ongoing treatment for patients with GORD. Thus, it would have slightly underestimated associations reported between GORD and oral manifestations, but it would pose a serious threat to the associations found. Also, some oral side effects of prescription could not be ruled out (such as the effect of proton-pump inhibitors on xerostomia). Sixth, we could not rule out the effect of other risk factors linked to xerostomia, such as: diabetes, hepatic disease or a side effect (although minor) of medication, including antihistamines, proton pump inhibitors, calcium channel blockers and beta-blockers.^{5 13 45} Further trials and clinical studies are needed to rule out these potential confounding risk factors. Future studies in humans should include biopsies of the oral epithelium to correlate clinical and histological findings. Our present findings (from [table 3](#)) suggest that the Montreal consensus recommendations should now be expanded to include aphthoid-ulcerative lesions, xerostomia, gingivitis, atrophic glossitis, angular cheilitis, OSF and candidiasis in the extraoesophageal symptomatology of GORD.^{2 44}

Dental health is widely neglected in Pakistan, where dental visits are restricted to a downstream approach (interventions at microlevel).^{47 53 54} Further, general practitioners and gastroenterologists are often the primary healthcare providers for patients with GORD, but while addressing their main GI concerns, the oral manifestations of these systemic conditions are often overlooked. This study highlights the need for dental referral in patients with upper GI disorders (in this case GORD), which can have a marked effect on both systemic and oral health.

CONCLUSION

This study reinforces DE as strong comorbidity of chronic and a severe form of GORD. Patients with DEs had severe oral symptoms and relatively more compromised oral health than did those without DE. We found a positive correlation between severe form of GORD and oral manifestations, such as xerostomia, aphthoid mucosal ulceration, gingivitis and angular cheilitis. Further, unhealthy

dietary patterns and frequent nausea/vomiting increase the likelihood of developing chronic GORD and DE, hence leading towards development of oral soft-tissue lesions, with increasing severity and compromised oral health. We recommend timely dental visits for evaluation of oral health, to assess the degree of oral manifestations, and prevent its progression. We also urge gastroenterologists to perform routine oral examinations and make referrals to a dentist to avoid worsening of the oral conditions caused by GORD.

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