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Original Research Article

Association of Long-term Proton Pump Inhibitor Use with Xerostomia, Taste Alteration and Denture Satisfaction: A Cross-Sectional Study

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Abstract: Objectives: To determine the relationship between use of long-term proton pump inhibitor (PPI) and xerostomia, taste change and denture satisfaction in removable denture users. ***Materials and Methods:*** The sample size of the cross-sectional study was 412 denture wearers (minimum age 40 years) who attended CMH Lahore Medical College Dental Hospital between January 2023 and November 2025. The respondents were divided into chronic PPI users (6 months of continuous use, n=156) and non-users (n=256). Xerostomia was measured through the use of the Summated Xerostomia Inventory (SXI-Dutch), taste changes were measured through a validated taste questionnaire and denture satisfaction as measured by a modified McGill Denture Satisfaction Instrument. Multivariable logistic regression that was adjusted to age, gender, diabetes, type of denture, polypharmacy and smoking status. Findings: PPI users were much more likely to report moderate-severe xerostomia (68.6% vs 29.3% p=0.001), taste changes (56.4% vs 28.1% p=0.001) and low denture satisfaction (48.1% vs 24.6% p=0.001) than non-users. The PPI use was also found to be independently related with xerostomia (adjusted OR=4.12, 95%CI: 2.68-6.34, p<0.001), taste changes (aOR=3.18, 95%CI: 2.06-4.91, p<0.001), and low denture satisfaction (aOR=2.64, 95%CI: 1.72-4.06, p<0.001). PPI time of use exhibited dose-response correlation with the severity of xerostomia (p-trend<0.001). ***Conclusions:*** The use of PPI in the long-term is strongly related to xerostomia, taste changes, and a lack of denture satisfaction. The clinicians should bear in mind these oral complications when giving PPIs, especially in edentulous patients who have to undergo the rehabilitation using prosthetic materials. Clinical Significance: The present study demonstrates significant clinical implications of oral health of chronic PPI therapy in denture users where review of medication and interprofessional communication between dentists and physicians is vital.

Keywords: Denture satisfaction, proton pump inhibitors, taste perception, xerostomia, removable prosthesis, oral health

INTRODUCTION

Proton pump inhibitors (PPIs) are widely prescribed drugs all over the world, and are most commonly used to treat gastroesophageal reflux disease (GERD), peptic ulcer disease, and dyspepsia.[1, 2] The global use of PPIs has been more than enough to reach 113 million people in the world, and the usage rates of these medications are still rising in the older population [3,4].

Although PPIs are usually deemed safe to use in short-term, accumulating evidence indicates that prolonged PPI treatment could be linked to a range of adverse outcomes such as Clostridium difficile infections, community-acquired pneumonia, fractures, chronic kidney diseases, nutritional

deficiencies, etc [5-7]. Notably, the recent studies have also suggested that PPI treatment can be associated with oral complications, including salivary dysfunction, changes in the oral microbiome, and dental caries [8-10].

Xerostomia, which is a subjective perception of dry mouth, is a frequent complaint in older adults, and it can have an enormous impact on oral health-related quality of life.[12],[13] There are many factors that cause xerostomia including age, systemic illnesses (especially diabetes), drugs, and Sjögren syndrome.[11],[12] Multiple drugs are linked with salivary dysfunction and are called reversible causes.
For denture wearers, adequate salivary function is crucial for denture retention, comfort, and function.[16] Saliva provides lubrication between denture and mucosa, aids in denture adhesion through surface tension and viscosity, and protects oral mucosa from mechanical trauma.[17] Xerostomia in denture wearers can lead to reduced retention, increased friction, mucosal ulceration, difficulty speaking and eating, and ultimately decreased denture satisfaction and quality of life.[18],[19]

The pathway through which PPIs may cause xerostomia is not thoroughly known. Suggested mechanisms are: (1) disruption of the absorption of vitamin B 12 and magnesium, both of which are needed in the salivary gland[20],[21]; (2) possible direct impacts on H+/K+ -ATPase in salivary glands, which is however controversial. [22]; (3) changes in oral and gut microbiome which may have an indirect impact on oral health [23]; and (4) drug-induced immunological changes affecting salivary tissue.[24]

Another important factor that influences the nutritional intake and the quality of life is taste perception. There have been a number of studies with taste disturbances as negative consequences of PPI treatment but the prevalence and pathogenesis of these effects is not well understood. [25, 26] PPIs can disrupt taste by depleting zinc, changing salivary composition, or acting directly on taste receptors. [27]
In denture wearers who experience diminished masticatory performance and altered oral sensation as a result of palatal coverage, further taste disturbances can have a marked adverse effect on food enjoyment and nutritional status[28].

Although the prevalence of both PPI use and denture wearing among the aging populations is very high, very little study has specifically touched their intersection. PPI related oral effects have mostly been investigated using dental caries, oral infections or bone metabolism of implant patients.[29–31] To our knowledge, no study has comprehensively evaluated the association between chronic PPI use and the triad of xerostomia, taste alterations, and denture satisfaction in a denture-wearing population.
In Pakistan, PPIs are widely available over-the-counter and are frequently used without medical supervision, often for extended periods.[32] This unregulated use pattern, combined with high rates of edentulism (approximately 46% in adults over 65 years) and limited awareness of medication-related oral complications, creates a particularly vulnerable population.[33],[34]
Therefore, the aim of this study was to investigate the association between long-term PPI use and xerostomia, taste alterations, and denture satisfaction among complete and partial removable denture wearers attending a tertiary care dental hospital in Pakistan. We hypothesized that chronic PPI users would have higher prevalence of xerostomia, taste disturbances, and lower denture satisfaction compared to non-users, independent of other risk factors.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was a cross-sectional observational study done in the Department of Prosthodontics, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan, during the period of January 2024 and November 2025. Informed consent was taken through written consent. This paper was based on the STROBE guidelines of observational studies reporting.[35]

2.2 | Study population and sampling

The study population consisted of patients attending the prosthodontic clinics for denture maintenance or new denture fabrication. Sample size was calculated using the formula for comparing two proportions, assuming a xerostomia prevalence of 30% in non-PPI users and 50% in PPI users (based on pilot data), with α=0.05, power=80%, and 1:1.5 ratio of exposed to unexposed, yielding a minimum required sample of 368 participants. Accounting for 10% incomplete responses, we aimed to recruit 410 participants.

Inclusion criteria:

- Age ≥40 years
- Wearing removable complete or partial dentures for ≥6 months
- Ability to understand and complete questionnaires in Urdu or English
- Availability of complete medical and medication history

Exclusion criteria:

- History of head and neck radiotherapy

- Diagnosed Sjögren's syndrome or other autoimmune diseases affecting salivary glands
- Current chemotherapy
- Use of medications causing severe xerostomia (anticholinergics, tricyclic antidepressants) within the past 3 months
- Active oral infections or malignancies
- Severe cognitive impairment preventing questionnaire completion
- Alcohol or substance abuse

2.3 | Data collection

Data were collected through structured face-to-face interviews conducted by two calibrated examiners (inter-examiner reliability κ=0.87 for xerostomia assessment). A standardized questionnaire captured:

Demographic and medical information:

- Age, gender, education level, socioeconomic status
- Medical history: diabetes mellitus, hypertension, cardiovascular disease, thyroid disorders
- Complete medication history including all prescription and over-the-counter drugs
- Smoking status (never, former, current) and pack-years if applicable
- Alcohol consumption

PPI exposure: Participants were classified as:

- **Chronic PPI users:** Continuous use of any PPI (omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole) for ≥6 months. Information collected included: type of PPI, daily dose, duration of use, indication for use, and prescriber (physician, self-medication).
- **Non-PPI users:** No PPI use or use for <1 month more than 1 year before assessment.

Participants with PPI use between 1-6 months or intermittent use were excluded from analysis to ensure clear group distinction.

Denture-related information:

- Type of denture (complete maxillary/mandibular, partial removable)
- Duration of current denture use
- Previous denture experience
- Frequency of denture cleaning
- Night-time denture removal habits

2.4 | Outcome measures

2.4.1 | Xerostomia assessment

Xerostomia was evaluated using the validated Summated Xerostomia Inventory (SXI-Dutch), translated and culturally adapted to Urdu.[36] The SXI consists of 5 items assessing:

1. Difficulty eating dry foods
2. Mouth feels dry when eating meals
3. Getting up at night to drink
4. Mouth feels dry
5. Difficulty swallowing certain foods

Each item is scored on a 5-point Likert scale (1=never, 2=hardly ever, 3=occasionally, 4=often, 5=very often). Total scores range from 5-25, with higher scores indicating more severe xerostomia. Scores were categorized as: normal/mild (5-12), moderate (13-18), severe (19-25).[37]

2.4.2 | Taste alteration assessment

Taste alterations were assessed using a structured questionnaire adapted from the validated Taste and Smell Survey.[38] The questionnaire included 8 items evaluating:

1. Change in ability to taste sweet foods
2. Change in ability to taste salty foods
3. Change in ability to taste sour foods
4. Change in ability to taste bitter foods
5. Persistent unusual or unpleasant taste
6. Overall reduction in taste ability
7. Reduced ability to distinguish different tastes
8. Impact on food enjoyment

Each item was scored 0-2 (0=no change, 1=mild change, 2=significant change). A composite taste alteration score (0-16) was calculated. Clinically significant taste alteration was defined as a score ≥5, based on receiver operating characteristic (ROC) curve analysis correlating with patient-reported taste problems affecting diet.

2.4.3 | Denture satisfaction assessment

Denture satisfaction was evaluated using a modified McGill Denture Satisfaction Instrument, culturally adapted for Pakistani population.[39] The instrument assessed 9 domains:

1. General satisfaction
2. Ability to chew
3. Comfort during eating

4. Ability to speak
5. Aesthetics/appearance
6. Ease of cleaning
7. Retention and stability
8. Comfort without eating
9. Effect on social activities

Each domain was scored on a 5-point Likert scale (1=very dissatisfied, 5=very satisfied). Total scores ranged from 9-45. Denture satisfaction was categorized as: low (<27), moderate (27-36), high (>36).[40]

2.5 | Clinical examination

A standardized clinical examination was performed by a single calibrated prosthodontist to assess:

- Oral mucosal health (ulcerations, erythema, denture stomatitis)
- Denture condition (retention, stability, occlusion, vertical dimension)
- Residual ridge resorption (assessed using Atwood classification)[41]
- Tongue characteristics (fissuring, coating, atrophy)

2.6 | Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM Corp, Armonk, NY, USA) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were tested for normality using Shapiro-Wilk test and reported as mean±standard deviation (SD) or median (interquartile range [IQR]) as appropriate. Categorical variables were presented as frequencies and percentages.

Bivariate analysis: Differences between PPI users and non-users were assessed using independent t-tests or Mann-Whitney U tests for continuous variables, and chi-square tests or Fisher's exact tests for categorical variables.

Multivariable analysis: Binary logistic regression was performed to examine associations between PPI use and each outcome (moderate-to-severe xerostomia, clinically significant taste alteration, low denture satisfaction). Three models were constructed:

- **Model 1:** Unadjusted
- **Model 2:** Adjusted for age and gender
- **Model 3:** Fully adjusted model including age, gender, diabetes status, denture type (complete vs partial), polypharmacy (≥5 medications), and smoking status

Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

Dose-response analysis: Associations between duration of PPI use (categorized as 6-12 months, 1-2 years, 2-5 years, >5 years) and outcomes were examined using logistic regression. Linear trend tests were performed by including duration as a continuous variable.

Subgroup analyses: Stratified analyses were conducted by:

- Denture type (complete vs partial dentures)
- Diabetes status (diabetic vs non-diabetic)
- Age group (<65 years vs ≥65 years)
- PPI duration (<2 years vs ≥2 years)

Sensitivity analyses: To test robustness of findings, we performed sensitivity analyses:

1. Excluding participants with diabetes
2. Excluding participants taking ≥5 medications
3. Using alternative cutoffs for outcome categorization
4. Using complete-case analysis vs multiple imputation for missing data (<3%)

Statistical significance was set at $p<0.05$ (two-tailed). Multiple testing adjustment was not applied as outcomes were biologically related and analyses were hypothesis-driven rather than exploratory.

RESULT

3.1 | Participant characteristics

A total of 468 denture wearers were screened for eligibility. Of these, 56 were excluded (22 for Sjögren's syndrome or autoimmune disease, 18 for concurrent anticholinergic medication use, 8 for active oral malignancy, 6 for severe cognitive impairment, and 2 declined participation). The final study population comprised 412 participants: 156 chronic PPI users (37.9%) and 256 non-PPI users (62.1%).

Table 1 summarizes baseline characteristics. PPI users were significantly older (mean age 64.8±10.4 vs 60.2±11.8 years, $p<0.001$), had higher prevalence of diabetes (52.6% vs 28.5%, $p<0.001$), hypertension (68.6% vs 42.2%, $p<0.001$), and cardiovascular disease (24.4% vs 11.3%, $p=0.001$). PPI users also took significantly more concurrent

medications (median 4 [IQR 3-6] vs 2 [IQR 1-3], p<0.001). There were no significant differences in gender distribution, education level, denture type, or smoking status between groups.

TABLE 1 | Baseline characteristics of study participants

Characteristic	All participants (n=412)	PPI users (n=156)	Non-PPI users (n=256)	p-value
Demographics				
Age (years), mean±SD	61.9±11.4	64.8±10.4	60.2±11.8	<0.001
Female, n (%)	246 (59.7)	97 (62.2)	149 (58.2)	0.425
Education level, n (%)				0.312
- None/primary	168 (40.8)	68 (43.6)	100 (39.1)	
- Secondary	152 (36.9)	54 (34.6)	98 (38.3)	
- Higher education	92 (22.3)	34 (21.8)	58 (22.7)	
Medical comorbidities				
Diabetes mellitus, n (%)	155 (37.6)	82 (52.6)	73 (28.5)	<0.001
Hypertension, n (%)	215 (52.2)	107 (68.6)	108 (42.2)	<0.001
Cardiovascular disease, n (%)	67 (16.3)	38 (24.4)	29 (11.3)	0.001
Thyroid disorders, n (%)	54 (13.1)	24 (15.4)	30 (11.7)	0.291
Medication use				
Number of medications, median (IQR)	3 (1-5)	4 (3-6)	2 (1-3)	<0.001
Polypharmacy (≥5 drugs), n (%)	124 (30.1)	72 (46.2)	52 (20.3)	<0.001
Antihypertensive drugs, n (%)	198 (48.1)	102 (65.4)	96 (37.5)	<0.001
Antidiabetic drugs, n (%)	142 (34.5)	76 (48.7)	66 (25.8)	<0.001
Lifestyle factors				
Smoking status, n (%)				0.186
- Never smoker	318 (77.2)	116 (74.4)	202 (78.9)	
- Former smoker	58 (14.1)	26 (16.7)	32 (12.5)	
- Current smoker	36 (8.7)	14 (9.0)	22 (8.6)	
Denture characteristics				
Complete dentures, n (%)	268 (65.0)	106 (67.9)	162 (63.3)	0.341
Partial dentures, n (%)	144 (35.0)	50 (32.1)	94 (36.7)	0.341
Duration of denture use (months), median (IQR)	24 (12-48)	30 (12-60)	24 (12-42)	0.092
Previous denture experience, n (%)	194 (47.1)	78 (50.0)	116 (45.3)	0.357
PPI characteristics				
PPI type, n (%)				
- Omeprazole	—	68 (43.6)	—	
- Pantoprazole	—	54 (34.6)	—	
- Esomeprazole	—	22 (14.1)	—	
- Rabeprazole	—	12 (7.7)	—	
Duration of PPI use (months), median (IQR)	—	30 (12-60)	—	
Indication for PPI, n (%)				
- GERD/acid reflux	—	102 (65.4)	—	
- Peptic ulcer disease	—	28 (17.9)	—	
- Dyspepsia	—	18 (11.5)	—	
- Prophylaxis (NSAID use)	—	8 (5.1)	—	
PPI prescribed by physician, n (%)	—	124 (79.5)	—	

Characteristic	All participants (n=412)	PPI users (n=156)	Non-PPI users (n=256)	p-value
Self-medication, n (%)	—	32 (20.5)	—	

Data are presented as mean±SD, median (IQR), or n (%). PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; IQR, interquartile range.

3.2 | Primary outcomes

3.2.1 | Xerostomia

PPI users had significantly higher mean SXI scores compared to non-users (15.8±5.6 vs 10.4±4.2, p<0.001) (**Table 2**). The prevalence of moderate-to-severe xerostomia was 68.6% in PPI users versus 29.3% in non-users (p<0.001). Individual SXI item analysis showed PPI users reported significantly more problems with all five components: difficulty eating dry foods (3.4±1.2 vs 2.2±1.1, p<0.001), mouth dryness during meals (3.2±1.3 vs 2.1±1.0, p<0.001), waking at night to drink (3.1±1.4 vs 1.9±1.2, p<0.001), general mouth dryness (3.3±1.2 vs 2.1±1.1, p<0.001), and swallowing difficulties (2.8±1.3 vs 2.1±1.0, p<0.001).

TABLE 2 | Comparison of outcome measures between PPI users and non-users

Outcome	PPI users (n=156)	Non-PPI users (n=256)	p-value
Xerostomia			
SXI total score, mean±SD	15.8±5.6	10.4±4.2	<0.001
SXI categories, n (%)			<0.001
- Normal/mild (5-12)	49 (31.4)	181 (70.7)	
- Moderate (13-18)	72 (46.2)	62 (24.2)	
- Severe (19-25)	35 (22.4)	13 (5.1)	
Moderate-to-severe xerostomia, n (%)	107 (68.6)	75 (29.3)	<0.001
Taste alteration			
Taste score, mean±SD	6.8±3.4	3.6±2.8	<0.001
Clinically significant taste alteration (score ≥5), n (%)	88 (56.4)	72 (28.1)	<0.001
Individual taste changes, n (%)			
- Sweet taste alteration	54 (34.6)	48 (18.8)	<0.001
- Salty taste alteration	62 (39.7)	52 (20.3)	<0.001
- Sour taste alteration	48 (30.8)	38 (14.8)	<0.001
- Bitter taste alteration	44 (28.2)	32 (12.5)	<0.001
- Persistent unusual taste	58 (37.2)	42 (16.4)	<0.001
- Reduced food enjoyment	76 (48.7)	56 (21.9)	<0.001
Denture satisfaction			
Total satisfaction score, mean±SD	24.6±7.2	29.8±6.4	<0.001
Satisfaction categories, n (%)			<0.001
- Low (<27)	75 (48.1)	63 (24.6)	
- Moderate (27-36)	62 (39.7)	128 (50.0)	
- High (>36)	19 (12.2)	65 (25.4)	
Low denture satisfaction, n (%)	75 (48.1)	63 (24.6)	<0.001
Domain-specific satisfaction, mean±SD			
- General satisfaction	2.6±0.9	3.4±0.8	<0.001
- Ability to chew	2.4±1.0	3.2±0.9	<0.001
- Comfort during eating	2.5±0.9	3.3±0.8	<0.001
- Ability to speak	2.8±0.9	3.4±0.8	<0.001
- Aesthetics	3.2±0.8	3.6±0.7	<0.001

Outcome	PPI users (n=156)	Non-PPI users (n=256)	p-value
- Ease of cleaning	3.4±0.8	3.6±0.7	0.008
- Retention/stability	2.3±1.0	3.1±0.9	<0.001
- Comfort without eating	2.7±0.9	3.4±0.8	<0.001
- Social activities	2.7±1.0	3.4±0.9	<0.001

SXI, Summated Xerostomia Inventory; PPI, proton pump inhibitor; SD, standard deviation.

3.2.2 | Taste alterations

PPI users had significantly higher taste alteration scores (6.8±3.4 vs 3.6±2.8, p<0.001). Clinically significant taste alterations were present in 56.4% of PPI users compared to 28.1% of non-users (p<0.001). All individual taste modalities (sweet, salty, sour, bitter) showed higher rates of alteration in PPI users, with the most pronounced effects on salty (39.7% vs 20.3%, p<0.001) and sweet (34.6% vs 18.8%, p<0.001) taste perception.

3.2.3 | Denture satisfaction

PPI users reported significantly lower denture satisfaction scores (24.6±7.2 vs 29.8±6.4, p<0.001). Low denture satisfaction was observed in 48.1% of PPI users versus 24.6% of non-users (p<0.001). Domain-specific analysis revealed that PPI users were particularly dissatisfied with retention/stability (2.3±1.0 vs 3.1±0.9), ability to chew (2.4±1.0 vs 3.2±0.9), and comfort during eating (2.5±0.9 vs 3.3±0.8) (all p<0.001).

3.3 | Multivariable regression analysis

Table 3 shows findings of multivariate logistic regression. On unadjusted analysis (Model 1), the use of PPI was significantly related to the three outcomes. PPI use was independently associated with, after complete adjustment to possible confounders (Model 3):

- Moderate-to-severe xerostomia: aOR=4.12 (95%CI: 2.68-6.34), p<0.001
- Clinically significant taste alteration: aOR=3.18 (95%CI: 2.06-4.91), p<0.001
- Low denture satisfaction: aOR=2.64 (95%CI: 1.72-4.06), p<0.001

Other significant predictors in fully adjusted models included diabetes (associated with xerostomia and low denture satisfaction), older age (associated with xerostomia), and complete dentures versus partial dentures (associated with low satisfaction).

TABLE 3 | Multivariable logistic regression: Association between PPI use and outcomes

Outcome	Model 1 (Unadjusted)	Model 2 (Age, gender adjusted)	Model 3 (Fully adjusted)[a]
Moderate-to-severe xerostomia			
OR (95% CI)	5.24 (3.52-7.79)	4.86 (3.22-7.33)	4.12 (2.68-6.34)
p-value	<0.001	<0.001	<0.001
Clinically significant taste alteration			
OR (95% CI)	3.32 (2.22-4.97)	3.28 (2.17-4.96)	3.18 (2.06-4.91)
p-value	<0.001	<0.001	<0.001
Low denture satisfaction			
OR (95% CI)	2.84 (1.88-4.29)	2.72 (1.78-4.16)	2.64 (1.72-4.06)
p-value	<0.001	<0.001	<0.001

OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor. [a]Model 3 adjusted for age, gender, diabetes mellitus, denture type (complete vs partial), polypharmacy (≥5 medications), and smoking status.

3.4 | Dose-response relationship

Analysis of PPI duration revealed a clear dose-response relationship with xerostomia severity (p-trend<0.001) (**Figure 3**). Compared to non-users, adjusted ORs for moderate-to-severe xerostomia were:

- 6-12 months PPI use: aOR=2.48 (95%CI: 1.22-5.04)
- 1-2 years: aOR=3.86 (95%CI: 2.12-7.02)
- 2-5 years: aOR=5.12 (95%CI: 2.94-8.92)
- 5 years: aOR=6.84 (95%CI: 3.48-13.45)

Similar trends were observed for taste alterations (p-trend=0.002) and denture satisfaction (p-trend=0.008), though less pronounced.

3.5 | Subgroup and sensitivity analyses

Subgroup analyses (**Table 4**) demonstrated consistent associations across most strata. The association between PPI use and xerostomia was stronger in:

- Complete denture wearers (aOR=4.86, 95%CI: 2.94-8.02) versus partial denture wearers (aOR=2.94, 95%CI: 1.52-5.68), though interaction was not significant (p-interaction=0.164)
- Diabetic patients (aOR=5.42, 95%CI: 2.86-10.28) versus non-diabetic (aOR=3.24, 95%CI: 1.94-5.42), p-interaction=0.086
- Older patients ≥65 years (aOR=5.18, 95%CI: 2.98-9.00) versus younger <65 years (aOR=3.22, 95%CI: 1.84-5.64), p-interaction=0.122

TABLE 4 | Subgroup analyses: Association between PPI use and moderate-to-severe xerostomia

Subgroup	n	PPI users with outcome, n (%)	Non-users with outcome, n (%)	Adjusted OR[a] (95% CI)	p-value	p-interaction[b]
Denture type						0.164
Complete dentures	268	76/106 (71.7)	52/162 (32.1)	4.86 (2.94-8.02)	<0.001	
Partial dentures	144	31/50 (62.0)	23/94 (24.5)	2.94 (1.52-5.68)	0.001	
Diabetes status						0.086
Diabetic	155	62/82 (75.6)	28/73 (38.4)	5.42 (2.86-10.28)	<0.001	
Non-diabetic	257	45/74 (60.8)	47/183 (25.7)	3.24 (1.94-5.42)	<0.001	
Age group						0.122
<65 years	224	52/86 (60.5)	44/138 (31.9)	3.22 (1.84-5.64)	<0.001	
≥65 years	188	55/70 (78.6)	31/118 (26.3)	5.18 (2.98-9.00)	<0.001	
PPI duration						0.008
<2 years	86	48/86 (55.8)	75/256 (29.3)	2.94 (1.76-4.92)	<0.001	
≥2 years	70	59/70 (84.3)	75/256 (29.3)	6.28 (3.24-12.18)	<0.001	

OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor. [a]Adjusted for age, gender, diabetes mellitus, denture type, polypharmacy, and smoking status (excluding the stratifying variable). [b]p-interaction tests whether the association between PPI use and outcome differs significantly across subgroups.

Sensitivity analyses confirmed robustness of findings:

1. Excluding diabetic patients: aOR for xerostomia=3.24 (95%CI: 1.94-5.42)
2. Excluding polypharmacy patients: aOR for xerostomia=3.68 (95%CI: 2.18-6.21)
3. Using SXI cutoff ≥15 for severe xerostomia: aOR=5.42 (95%CI: 3.12-9.42)
4. Complete-case analysis (excluding 8 participants with any missing data): results virtually unchanged

3.6 | Clinical examination findings

Clinical examination revealed higher prevalence of oral mucosal changes in PPI users: denture stomatitis (32.1% vs 18.8%, p=0.002), angular cheilitis (14.1% vs 7.0%, p=0.020), and fissured tongue (28.2% vs 16.4%, p=0.006). Tongue coating was also more common in PPI users (41.0% vs 25.4%, p=0.001).

DISCUSSION

This cross-sectional research examined relationships between long time PPI usage and xerostomia, taste changes and denture satisfaction in a group of Pakistani denture wearers. The key results were that the chronic use of PPI was significantly correlated with about 4- fold higher likelihood of moderate-severe xerostomia, 3-fold higher probability of taste changes, and 2.6-fold higher probability of low denture satisfaction, after consideration of various confounding factors (age, diabetes, and polypharmacy). These relationships demonstrated dose-response correlations between the duration of PPI use and across various subgroups and sensitivity analyses.

4.1 | Xerostomia findings in context

The prevalence of moderate-to-severe xerostomia in our PPI users (68.6%) substantially exceeds rates reported in general populations (10-40%)[11,12] and even in typical denture-wearing populations (30-50%).[13] While some studies have reported associations between PPI use and dry mouth symptoms,[42,43] few have quantified this association in denture wearers using validated instruments. A Dutch study by Wolff et al[44] found PPI use associated with 2.1-fold increased odds of xerostomia in elderly populations, lower than our 4.1-fold increase, possibly reflecting our specific focus on denture wearers who may be more vulnerable to medication-induced salivary dysfunction.

A number of mechanisms support the biological plausibility of xerostomia caused by PPI. First, chronic PPI use impairs absorption of vitamin B_{12} and magnesium through sustained gastric acid suppression.[20,21] Both micronutrients are essential for normal salivary gland function: vitamin B_{12} is required for cellular metabolism and DNA synthesis in secretory cells, while magnesium serves as a cofactor for numerous enzymatic reactions.[45] Deficiency of either can compromise salivary gland function. Second, some evidence suggests PPIs may directly affect H^+/K^+-ATPase pumps in salivary tissue, though salivary glands primarily express different ATPase isoforms than gastric parietal cells, making this mechanism controversial.[22] Third, PPIs profoundly alter the gut microbiome[23] and may similarly affect oral microbiome composition, potentially contributing to oral dysbiosis and inflammatory changes affecting salivary function.[46]
The dose-response correlation that we have found, i.e., the longer the PPI lasts, the greater the risk of xerostomia, further supports the argument of causality. This observation implies long-term acid suppressive effects and/or degradative effects on micronutrients. It is interesting to note that PPI use, even in term of relatively short-period (6-12 months), was already linked to higher risk of xerostomia, which demonstrates that the negative consequences might appear sooner than commonly expected.

4.2 | Taste alteration findings

The fact that 56.4% of the PPI users had clinically significant changes in tastes is a valuable contribution to the literature. Although a case report and pharmacovigilance data have reported the occurrence of taste disturbances with PPIs, 25, 26, not many studies have quantified this relationship systematically. A trial of 7-14 percent of PPI users by Schenck27 showed taste disturbances, which is much less than our result, which could be due to systematic questionnaires and not spontaneous reporting, and a population (denture wearers) already prone to taste disturbance.

The various mechanisms by which PPI can impact on taste involve several mechanisms 47. The issue of zinc depletion is also particularly pertinent, and the effects of PPIs on gastric pH and intrinsic factor can decrease zinc absorption 48, which is important in taste receptor functioning, gustin 49 (salivary protein critical in taste bud development) production, and rapid turnover of taste cells 50.

In denture wearers, there is a problem of taste disturbances to add limb to existing difficulties 28. Dentures, especially complete maxillary dentures, also decrease the sense of taste by blocking palatal taste receptors and by changing contact with oral mucosa by food, which may lead to a severe worsening of nutritional status and life quality in older people who already face the risk of malnutrition 51.

4.3 | Denture satisfaction implications

Clinical implications of the association between PPI use and denture dissatisfaction (48.1% vs 24.6% with low satisfaction) are direct. Domain analysis PPI users were not satisfied with retention/stability, chewing ability, and comfort, especially areas that significantly require proper salivary functioning. This trend is a significant indicator that xerostomia is a mediator.
Saliva is also crucial to the function of dentures by several mechanisms.[16,17] It decreases friction

between denture and the mucosa by providing lubrication, increases retention by acting through surface tension and viscosity effects and prevents mechanical trauma to the mucosa. All these functions are impaired by Xerostomia. A number of studies have reported the relationships between decreased salivary flow and denture issues.[18],[19] Our study adds to these previous studies by determining that PPI use is a distinct, potentially manipulable risk factor that is associated with denture dissatisfaction.
It makes sense that the complete denture wearers exhibited stronger relationships compared to the partial denture wearers because complete dentures rely more on the salivary film to be retained and functional. This difference effect can inform clinical decision-making on PPI necessity in various denture-wearing groups.

4.4 | Clinical and public health implications
Our findings have several important practical implications:
1. The use of medication in patients with dentures: The use of PPI should be regularly checked by the dentist when a patient presents to the dentist. The use of PPI must be viewed as a possible contributing factor when the patients appear with xerostomia, denture discomfort, or decreased satisfaction. This is especially applicable in such an environment as Pakistan where the prevalence of over-the-counter PPI results in the extensive, mostly unnecessary, chronic consumption 32.

2. Interprofessional communication: Our results highlight the necessity of dental and medical practitioner communication. When dentists realize that PPI users have xerostomia, they are supposed to inform prescribing physicians to reevaluate the need of using PPI. Most patients take PPIs outside the recommended clinical issue or even without suitable reasons 52, and these are chances to deprescribe.
3. PPI stewardship: The dose response relationship that we have observed is supportive of evidence-based strategies which suggest the lowest effective doses of PPI taking the shortest time possible. 53 Periodic review of current PPI need is important. Other remedies such as lifestyle changes, H 2 - receptors or antacids may be suitable in patients with mild symptoms of GERD.

4. Prevention: In case the patients need long term PPI treatment, a number of palliative interventions can alleviate xerostomia. They are: (a) maintaining proper hydration; (b) the use of saliva substitute or stimulants (b); using sugar-free gum or candy to increase salivary flow; (c) maximizing denture care to avoid secondary complications; (d) the possibility of vitamin B 12 / magnesium supplementation, but the evidence on this is not sufficient.
5. Patient education: Patients need to be made aware of possible side effects of PPIs on the oral side such as dry mouth and changes in taste 54. This fact allows to make an informed consent and helps patients to discuss the symptoms in time.

6. Denture design considerations: In the case of PPI users with xerostomia, a prosthodontist may wish to design the denture with fewer palatal covers where possible, to maximize denture extension and border seal or to add saliva reservoirs to denture design 55.

4.5 | Comparison with existing literature
Our findings align with and extend existing evidence on PPI-related oral complications. Several studies have documented increased risk of oral infections (particularly candidiasis) with PPI use.[8],[9] Bavishi and Dupont[56] reported 74% increased odds of oral candidiasis in PPI users, attributed to altered oral pH and microbiome changes. Our clinical findings of increased denture stomatitis in PPI users (32.1% vs 18.8%) are consistent with this literature.

Research on PPIs and dental caries has yielded mixed results. Some studies suggest increased caries risk,[10] potentially through xerostomia-mediated reduction in salivary buffering and antimicrobial properties. However, other studies found no association,[57] possibly reflecting differences in PPI duration, dental hygiene practices, or fluoride exposure across populations.

Our findings contrast with a recent study by Romandini et al[58] that reported protective effects of PPIs against peri-implantitis, attributed to anti-inflammatory properties. This apparent contradiction may reflect different mechanisms in implant osseointegration versus soft tissue/salivary function, or differences between implant-supported and mucosa-supported prostheses.

4.6 | Strengths and limitations
The strengths of the study are: (1) relatively large sample size that has provided adequate power; (2) validated instruments used to measure outcomes; (3) multiple confounders, such as diabetes, polypharmacy, and smoking, have been adequately adjusted and the strength of the study has been demonstrated to be strong; (4) the study has shown dose-response relationships that strengthen the cause and effect relationship; (5) all subgroups with consistency have been reported in the study and sensitivity tests have been conducted indicating that the study is robust; (6) a relatively large population that is clinically relevant

Limitations should also be recognized. First, the cross-sectional design does not allow making conclusive causal inferences. Although the causality of our dose-response findings and biological plausibility is supported, residual confounding

cannot be ruled out. Better evidence would be given by prospective cohort studies that would involve baseline audits prior to PPI initiation. Preferably, randomized controlled trials of the rates of xerostomia patients randomizing to PPIs versus alternatives would prove causal relationship, but such trials would encounter ethical and feasible issues.

Second, patient-reported questionnaires, as opposed to objective measurements, were used to measure the outcomes. Though questionnaires are able to record clinically relevant patient experiences and have excellent validity, additional objective testing (salivary flow rate measurement, quantitative taste testing) would reinforce results. Nevertheless, unstimulated and stimulated whole saliva flow values, though objective have their own weaknesses such as high inter-individual variability and non-standardization.[59]

Third, we did not have specific information on the dosing of PPI and adherence to the dosing, and whether patients were taking PPIs every day or occasionally. This shortcoming did not allow finer dose-response studies. Such details such as doses, time of administration and adherence measures should be prospectively captured in future studies.

Fourth, we only controlled a number of confounders; some residual confounding may occur. To provide an example, we did not evaluate dietary patterns, caffeine intake, or psychological stress, none of which can be excluded as the potential reasons of xerostomia. The predisposing factors of which PPIs were prescribed (GERD, peptic ulcer) may influence the oral symptoms on their own, but the dose-response effect on the PPI duration poses the idea that it is not the only cause.

Fifth, we used one tertiary care facility as a study sample, which might have limited external validity. Teaching hospitals have several differences with the general population in terms of disease complexity, socioeconomic status, or health literacy. Nevertheless, our facility covers a wide range of people, such as military and civilian patients of different socioeconomic statuses, which contributes to a high representation level.

Sixth, there is the possibility of detection bias, in which the users of PPI may be more keen on body symptomatology in general and therefore more inclined to report xerostomia or taste alterations. Nevertheless, the pattern of associations (strongest with xerostomia, intermediate with taste, weakest with general denture satisfaction) is such that it is not likely that it was a mere reporting bias.

Seventh, patient self-report and medical records were used to get information on PPI use and medical history, which may have resulted in recall bias. Nevertheless, PPIs are unique drugs that patients usually recall and confirmation to medical records must have reduced wrong classification.

Lastly we have not evaluated other significant outcomes like the nutritional status, quality of life or oral health-related quality of life which could have been influenced by the xerostomia and taste changes we reported. These wider effects should be investigated in the future.

4.7 | Future research directions

Key areas of future research in our results are as follows:

Temporal associations and reversibility assessment on the discontinuation of PPI would be determined by prospective cohort studies that have baseline measurements prior to PPI initiation and followed up in sequence.

Causal and clinically useful evidence would be best demonstrated by intervention studies that assess the effectiveness of PPI deprescribing in improving xerostomia and denture satisfaction.

Biological knowledge would be improved by mechanistic studies that examine individual mechanisms by which PPIs influence the salivary functioning (micronutrient levels, salivary microbiome, inflammatory markers, salivary composition).

Comparison studies assessing the fact that various PPIs or various dosing regimens (daily vs on-demand) have dissimilar impact on oral results may be able to influence prescribing patterns.

Research that involves other populations such as those who use implant-supported prosthesis, institutionalized elderly, and those with various genetic backgrounds would contribute to the generalizability.

The argument in favour of PPI stewardship would be enhanced by the economic studies that would measure the healthcare costs incurred due to PPI-related oral complications (additional visits to dental offices, denture remakes, complications management).

Early intervention studies to determine whether preventive measures (saliva substitutes, micronutrient supplementation) can prevent PPI-related oral complications would determine effective management measures.

5 | CONCLUSIONS

This cross-sectional study has shown that the use of PPI over a long period of time is strongly and

independently related to the enhanced prevalence of xerostomia, changes in taste, and diminished denture satisfaction in a group of Pakistani denture wearers. The relationships between associations and PPI duration were dose-response relationships that were strong on diverse subgroups and sensitivity tests. There are notable clinical implications to be made out of these findings, and they include that judicious PPI prescribing, periodic evaluation of therapeutic need, extraprofessional interaction between dental and medical practitioners, and patient education regarding possible oral side effects are important. Healthcare providers must understand these oral implications of health especially among those who are dealing with elderly denture-wearing patients who often take PPIs. The provisional and interventional studies are required to determine the causality and effective measures in preventing or management of PPI-related oral complications.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest relevant to this study.

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