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MOLECULAR INSIGHTS INTO DYSBIOSIS OF THE ORAL MICROBIOME IN XEROSTOMIC PATIENTS: A MULTI-OMICS ASSESSMENT

Original Research

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ABSTRACT

Objective: The use of multi-omics in investigating the changes in the oral microbiome in relation to xerostomia and assessing the molecular evidence of microbial dysbiosis.

Methods: This is a prospective observational study that was carried out in a tertiary care teaching hospital Federal PGMI Lahore during the period of October 2023 to March 2024. One hundred and fifty adult subjects were recruited and there were xerostomics and non-xerostomics. The rate of unstimulated salivary flow was recorded at 24 h after recruitment and the saliva samples were collected in order to profile the microbiome. The metagenomic sequencing evaluated the microbial diversity and taxonomic composition whereas the targeted metabolomic and proteomic analyses verified the functional and inflammatory signatures. The clinical assessment and the salivary flow rate were used to draw a line between xerostomia and control groups. The correlation analysis and receiver operating characteristic (ROC) curves were used to study the associations between microbial diversity indices, key taxa abundance, and molecular markers. The p-value of 0.05 was regarded as statistically significant.

Results: Patients with xerostomia had much lower microbial diversity and a specific change in oral compositions of microorganisms than did controls. Opponents and acidogenic bacteria were found in relatively high number in xerostomia compared to commensal taxa ($p < 0.001$). Integration of multi-omics demonstrated that there were increased levels of inflammatory metabolites and distorted salivary protein city in xerostomic people. Dysbiosis indices were found to correlate with low rates of salivary flow and the severity of the symptoms. Combined multi-omics signatures performed poorly when assessed using ROC analysis, with a value of 1.00 indicating good performance at 12.5724 and a sensitivity at 79.5 and specificity at 75.0 ($P = 0.05$) (Azvi et al., 2015).

Conclusion: Xerostomia is connected to severe dental dysbiosis of microbiome in which taxonomic and functional changes exist. Multi-omics profiling offers a sound molecular platform on the interpretation of microbial variations relating to the disease and can be effective in predicting and managing early and specific xerostomia induced oral complications. More multicenter research should be conducted to confirm such biomarkers and determine their applications in clinical settings.

Keywords: Xerostomia, Oral microbiome Oral microbiome, Dysbiosis, Multi-omics, Metagenomics, Saliva.

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INTRODUCTION

The oral cavity exemplifies a hostile biological ecosystem, in which host tissues commerce with immune mediators, saliva and inherent microbiota to uphold wellness of the mouth and the whole body. Aromatic imbalance of this balance, especially when salivary flow is lowered may lead to susceptibility to mucosal pathology, opportunistic infections and inflammation. Drug-induced, disease-associated and lifestyle-based Xerostomia changes the biochemical and antimicrobial salivary profiles, which reduces oral microenvironment and enhances predisposition to dysbiosis and mucosal damage [1-3].

The buffering of acids, mechanical clearance as well as the provision of antimicrobial peptides, immunoglobulins and metabolic substrates are key functions of saliva used as a precursor defense against oral diseases. Changes in the salivary composition have been associated with oxidative stress, immune dysregulation as well as loss of the integrity of epithelia which affect the patterns of microbial colonization [4,5]. Oral pathological and studies on cancer awareness amongst South Asian people indicate that further salivary protective system weakening by persistent mucosal offenses, and environmental problems leads to increase in disease burden and load [6].

Oxidative stress and pathways of inflammatory signaling have become directly recognized as master bridges between metabolic derangements and tissue pathophysiology. It has been shown by experimental studies that redox imbalance is one of the causes of epithelial injury, distorted cellular metabolism as well as activation of immune processes which also applies to the case of oral mucosal homeostasis [7-9]. Moreover, metabolic diseases, including diabetes, dyslipidemia as well as chronic liver diseases, have been identified to have effects on protein synthesis, albumin concentration as well as inflammatory mediators, which, in turn, are likely to mediate the effects on salivary composition and microbial activity [10-12].

On the molecular level, the development of bioinformatics, transcriptomics, and epigenetic profiling have improved our knowledge of the interaction between hosts and microbes in various organ systems. It is well emphasized that translational studies, which find diagnostic and prognostic biomarkers are crucial in the integration of molecular data with clinical phenotypes [13,14]. These methods are specifically suitable in the case of oral diseases where the non-invasive sampling offers a chance to detect the disease earlier and stratify risks individually. additional lifestyle issues, such as food habits, contact with environmental insurances, and customary actions, also alter both oral and systemic inflammatory conditions.

Pakistan based population-based research has shown excellent relationships between the lifestyle pattern, metabolic derangement, and risk of chronic diseases, highlighting the importance of considering oral health in the context of the overall systems [15-17]. Also, the nutritional deficiency and dysregulation of iron metabolism have been suspected of the mucosal susceptibility and immune impairment, supporting the interrelatedness of the metabolic and microbial regulation [18].

The current research will set out to investigate biological and molecular changes in oral dysbiosis amongst xerostomic patients. Adopting a biochemical, inflammatory, and molecular approach, this research aims to add to the further comprehension of the disruption of the salivary ecosystem and the consequences on oral health, which may have an impact on non-invasive diagnosis and offers an opportunity to select the most effective therapeutic options.

METHODOLOGY

This prospective observational study was an attempt to find out the molecular changes and dysbiosis of the oral microbiome in xerostomic patients at a tertiary care hospital Federal PGMI Lahore within the period of October 2023 to March 2024. All participants gave informed consent and the institutional ethics review board gave its approval to the study.

The inclusion criteria included participants who were older than 18 years and had been clinically referred to have xerostomia or non-xerostomic controls. Those who had active oral infections or those who had taken antibiotics in the past four weeks, immunodeficiency disorders and those with severe systemic diseases were also locked out to reduce confounding factors. Consecutive sampling was used in recruiting 150 individuals who fit in the inclusion criteria. The sample size was estimated on the basis of the earlier researches that

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had evaluated correlations among the oral microbiome diversity indices and clinical parameters, using the openEpi version 3.0.0 software (Atlanta, GA, USA) with 80% power of the study, 95% confidence interval and a 5% margin of error.

Multi-omics analysis on all participants involved in the study was carried out an hour after unstimulated saliva was taken within 24 hours of recruitment. The rate of salivary flow was rated and clinical trials on xerostomia severity were taken. To profile the oral microbiome, metagenomic sequencing was used and to determine functional and inflammatory signatures, targeted metabolomic and proteomic analyses were used. The xerostomic and control groups were divided into participants on the basis of clinical assessment and salivary flow rate threshold. Multi-omics integration

Data integration was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and using the R software. Mean was used to show the quantitative variable with standard deviation (SD) and frequencies and percentages were used to show the categorical variables. Independent sample t-tests were conducted to compare groups whose variables were continuous and Chi-square tests were used to compare groups whose variables are categorical. The correlation coefficient (r) of Pearson was utilized to evaluate the correlation between the parameters of microbial diversity indices and the abundance of key taxa with clinical variables, including salivary flow rate and the degree of xerostomia. Multi-omics signature diagnostic Performance of multi-omics signatures in detecting xerostomia associated dysbiosis was assessed through Receiver Operating Characteristics (ROC) curve, where the area under the curve (AUC), sensitivity, and specificity were determined. The p-value of 0.05 was regarded as statistically significant.

RESULTS

The total number of participants was 150 (86 males 57.3% and 64 females 42.7%). The mean age of the participants was 50.8 +12.9 years. The clinical evaluation and the rate of unstimulated salivary flow divided the respective groups into xerostomic (n = 78) and non-xerostomic control groups (n = 72). **Table 1** satisfies the baseline demographic and laboratory data.

Table 1: Baseline Characteristics of Study Participants (n = 150)

Variable	Xerostomic (n = 78)	Control (n = 72)	Test used	Test value	p-value
Age (years)	51.2 ± 13.0	50.4 ± 12.8	t-test	t = 0.41	0.68
Male, n (%)	44 (56.4%)	42 (58.3%)	Chi-square	$x^2 = 0$	0.82
Female, n (%)	34 (43.6%)	30 (41.7%)	Chi-square	x	0.82
Salivary flow rate (mL/min)	0.12 ± 0.05	0.35 ± 0.08	t-test	t = -15.3	<0.001
Drink	1.8 ± 0.4	2.7 ± 0.5	t-test	t = -12.1	<0.001
Simpson index	0.45 ± 0.10	0.68 ± 0.09	t-test	t = -11.5	<0.001

The level of microbial diversity, salivary flow rate and loss in commensal oral taxa was widely lower in Xerostomic patients than in controls as shown in **Table 2**.

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Table 2: Correlation of Microbiome Dysbiosis Indices with Clinical Parameters

Marker	Pearson's r	Significance (p)
Salivary flow rate	+0.72	<0.001*
Xerostomia severity score	-0.69	<0.001*
Shannon index	+0.65	<0.001*
Simpson index	+0.61	0.002*

**Pearson correlation coefficient (r); *p < 0.05 indicates statistical significance; + = positive correlation*

ROC analysis showed that joint multi-omics dysbiosis signatures were discriminatory to determine xerostomia-linked microbial imbalance **(Table 3)**.

Table 3: Diagnoses

Marker	AUC	Sensitivity (%)	Specificity (%)
Combined multi-omics signature	0.83	79.5	75.0
Shannon index	0.78	75.6	71.2
Simpson	0.76	72.3	70.5

AUC = area under the receiver operating characteristic curve; Sensitivity = proportion of correctly identified xerostomic patients; Specificity = proportion of correctly identified controls

DISCUSSION

The current research paper identifies the major changes in oral microbial diversity and composition in xerostomia in patients, which indicates the clinical applicability of the dysbiosis as an indicator of salivary gland dysfunction. We find that the salivary flow rate, Shannon index, and Simpson index of xerostomic patients are lower than in their healthy control and that salivary secretion is an important factor essential in upholding the homeostasis of microbes in the mouth [19-21]. Saliva is also a source of mechanical cleansing, as well as antimicrobial elements and its depletion opens a niche that is more vulnerable to pathogenic growth, resulting in caries susceptibility, mucosal inflammation, and opportunistic infections [22-24].

The direct relationship between glandular performance and the richness of the microflora can be indicated with the correlations (salivary flow with alpha diversity indexes: Shannon index r = 0.65; Simpson index r = 0.61) and the negative correlation between salivary flow and the degree of xerostomia (r = 0.69). These are also consistent with the literature on autoimmune-mediated hyposalivation and dry mouth induced by drugs, in which the reduced volume of salivary production results in dysbiosis and consequential oral disease [25-27]. The current research points out the necessity of considering the microbial monitoring of patients with chronic xerostomia as a way of preventing the development of long-term complications [28-30].

It is noteworthy that our analysis with multi-omics gave us a detailed insight into the dysregulation of microbes by measuring both the compositional and functional changes at the same time. The findings using ROC analysis showed that the combined multi-omics disorders signatures could distinguish xerostomic and control patients with a high level of sensitivity and specificity (AUC = 0.83), which was better than alpha-diversity measures. These data confirm the hypothesis of using multi-dimensional microbial signatures as effective biomarkers of oral disease impairment [31-33]. The functional changes of the carbs like metabolism or the formation of biofilms and the interactions between the hosts and microbes indicate that the dysbiosis does not lie in the compositional shifts only but in critical metabolic and immunological processes [34,35].

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Clinical implications of depletion in the protective commensals which include Streptococcus, Veillonella and Actinomyces in xerostomic patients are important. These taxes generate metabolites which ensure the integrity of the mucosa, compete with the pathogens and regulate local immunity. Their destruction disturbs the balance of the ecology and predises people to infections and inflammatory reactions [36-38]. The observation is concordant with the previous observations that show that the lack of advantageous taxa in hyapositivation level corresponded to amplified prosperity of opportunistic bacteria, which can endanger oral mucosal hurt [39].

Additionally, the pathology of the systemic effect of oral dysbiosis is starting to be examined. Host immune responses are exposed to the salivary microbes, which can adjust the production of cytokines and system inflammation. Dysbiotic microbial metabolites have the potential to contribute to oxidative stress, dysfunctional endothelial activities, and low-grade endothelial dysfunction and systemic inflammatory conditions that can be related to oral health in general to the broader systemic outcomes [40,41]. Dysbiosis indices, as such, offer a manner of having a comprehensive perspective of microbial imbalance and its possible systemic consequences.

Translational Microbial profiling has a promising future in clinical settings, and this is emphasized in our study. Risk can be predicted by simple clinical measures, e.g. salivary flow, but by combining both multi-omics and simple clinical measures, one can be able to directly stratify patients and intervene early at risk. Diversions aimed at the functionality of salivary glands, such as salivary stimulants, hydration methods, and customized regimes of oral wellbeing, might replenish the equilibrium of microbes and resort to avoid secondary complications [42-44]. Furthermore, detection of microbial patterns peculiar to xerostomia can benefit the creation of selective probiotics or prebiotics, which could lead to the overall positive changes in the state of the mouth and the whole body [45,46].

Evidence of the mechanistic basis of observed dysbiosis includes evidence of how salivary hypofunction changes the nutrient availability and the concentration of immune factors, along with pH, within the oral cavity, all of which modify microbial ecology [47-49]. These results place emphasis on understanding xerostomia and not only as a symptom, but a pathological condition, whose effects are real because they involve microbial and metabolic homeostasis. Multi-omics technology is able to describe these complex interactions and provide knowledge on pathways that can be therapeutically mediated [50].

There are some limitations to our study, even though it is well built. The study design is cross-sectional, which does not provide causal inference, and the study may be affected by other potential confounding factors like diet, drug intake, and underlying systemic comorbidities which can also alter microbial composition. The longitudinal studies are necessary to monitor dysbiosis throughout the time, evaluate the effectiveness of interventions, and define whether the restoration of the microbes is associated with better clinical outcomes. Also, the study should be augmented with greater sample size and using multi-center cohorts to increase the generalizability of the findings and enable the validation of multi-omics signature as a biomarker of severity of xerostomia.

Overall, xerostomia is related to great microbial dysbiosis, less diversity, and disappearance of commensals, and is linked to clinical severity and salivary flow. Multi-omics signatures are versatile in predicting patients early, patient stratification, and probable treatment guidelines. The further investigation must be conducted in terms of longitudinal tracking, functional confirmation, and creation of interventions able to re-establish salivary activity as well as microbial homeostasis and provide the possibility of designing individualized oral healthcare approaches.

CONCLUSION

This study demonstrates that xerostomia is strongly associated with pronounced oral microbiome dysbiosis, characterized by reduced microbial diversity, enrichment of pathogenic taxa, and significant functional alterations reflected in inflammatory metabolites and salivary protein changes. The integration of metagenomic, metabolomic, and proteomic data provides compelling molecular evidence linking decreased salivary flow to both taxonomic and functional disruptions of the oral ecosystem. These multi-omics signatures show potential utility as biomarkers for early identification, risk stratification, and targeted management of xerostomia-related oral complications, although further large-scale, multicenter studies are required to validate their clinical applicability.

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AUTHOR CONTRIBUTIONS

Author	Contribution
Irum Naz	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muhammad Ali	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Akram*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published

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