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The Gut-Oral Axis: How Oral Dysbiosis Influences Systemic Inflammation and Chronic Diseases

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Abstract

Introduction: The gut-oral axis has emerged as a significant pathway linking oral microbiome disturbances to systemic inflammation and chronic diseases. This study aimed to investigate the association between oral dysbiosis, systemic inflammatory markers, and the prevalence of chronic inflammatory conditions.

Methodology: This cross-sectional study was conducted over 12 months at DHQ, Kohat. A total of 126 patients with at least one chronic disease (type 2 diabetes, cardiovascular disease, rheumatoid arthritis, or inflammatory bowel disease) were enrolled. Oral health status was assessed using clinical indices and saliva samples for microbial analysis. Systemic inflammation was evaluated via hs-CRP, IL-6, and TNF-α level. Statistical analyses included chi-square tests, Pearson correlation, and multivariate regression.

Results: Oral dysbiosis was present in 64.3% of participants. Dysbiosis was significantly associated with elevated hs-CRP (mean 5.8 ± 2.1 mg/L), IL-6 (14.6 ± 4.2 pg/mL), and TNF-α (18.1 ± 5.5 pg/mL) ($p < 0.001$). Patients with low Shannon diversity index (<2.0) showed markedly higher systemic inflammation. Oral hygiene parameters such as plaque index (PI ≥ 2) and bleeding on probing were independent predictors of dysbiosis ($p < 0.05$). Strong associations were noted between oral dysbiosis and type 2 diabetes ($p = 0.002$) and cardiovascular disease ($p = 0.005$), with weaker but notable links to rheumatoid arthritis.

Conclusion: Oral dysbiosis is significantly correlated with systemic inflammation and appears to influence the burden of chronic disease. Improving oral microbial health may offer a novel approach for reducing systemic inflammation and managing chronic inflammatory disorders.

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Introduction

The human body harbors a complex and dynamic community of microorganisms, collectively known as the microbiota, which plays a critical role in maintaining physiological homeostasis [1]. Among the most densely populated microbial ecosystems are the oral cavity and gastrointestinal tract, each hosting a unique but interconnected microbial community [2]. Traditionally, research has focused on these microbial niches in isolation; however, emerging evidence has illuminated the existence of a bidirectional relationship between them, commonly referred to as the gut-oral axis [3]. This axis represents a physiological and immunological pathway through which alterations in the oral microbiome may influence the gut microbiota and vice versa, thereby affecting systemic health [4].

The oral cavity is the gateway to the gastrointestinal tract and serves as the first point of contact for microbial, dietary, and environmental stimuli [5]. It contains over 700 species of bacteria, many of which are involved in maintaining oral and systemic health [6]. However, disruptions in the balance of this ecosystem a phenomenon known as oral dysbiosis can lead to the proliferation of pathogenic species such as Porphyromonas gingivalis, Fusobacterium nucleatum, and Treponema denticola [7]. These pathogens are known contributors to periodontal disease and have also been implicated in translocating to distant body sites via the bloodstream or through swallowed saliva, where they may influence the gut microbiota and trigger immune responses [8].

Recent studies suggest that oral dysbiosis may contribute to systemic inflammation through the continuous dissemination of pro-inflammatory cytokines, bacterial endotoxins (such as lipopolysaccharides), and microbial DNA [9]. These microbial products can compromise epithelial barriers, activate toll-like receptors, and stimulate chronic low-grade inflammation an underlying factor in the pathogenesis of a wide range of chronic diseases, including cardiovascular disease, type 2 diabetes mellitus, rheumatoid arthritis, and even neurodegenerative disorders like Alzheimer's disease [10]. Furthermore, there is increasing recognition that individuals with chronic periodontitis often exhibit concurrent gastrointestinal dysbiosis, suggesting a potential causal link mediated by the gut-oral axis [11].

Despite these associations, the gut-oral axis remains an underexplored frontier in human health. Most studies have independently examined the oral and gut microbiomes without fully addressing the interconnected pathways through which dysbiosis in one niche may influence systemic disease via inflammatory mechanisms [12]. The precise molecular mediators and immune responses bridging the oral microbiota to chronic systemic diseases are not yet fully delineated, necessitating a more integrative approach to microbiome research [13]. This article aims to explore the current understanding of the gut-oral axis by examining how oral dysbiosis influences systemic inflammation and contributes to the development of chronic diseases a connection that remains insufficiently addressed in existing literature.

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted at the Divisional Headquarters Hospital, Kohat. The study spanned a duration of 12 months, from March 2023 to February 2024. The purpose of the study was to investigate the role of oral dysbiosis in contributing to systemic inflammation and its association with chronic diseases through the gut-oral axis.

Sample Size and Sampling Technique

A total of 126 participants were enrolled using a purposive sampling technique. The sample size was calculated using the OpenEpi software for cross-sectional studies. Assuming a 95% confidence level, 5% margin of error, and an expected prevalence of oral dysbiosis in chronic disease patients at 40%, the estimated sample size required was 126. This was deemed adequate to ensure statistical reliability and detect meaningful associations between variables.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were participants, both male and female, aged between 18 and 65 years, who had been diagnosed with at least one chronic inflammatory disease, such as type 2 diabetes mellitus, cardiovascular disease,

rheumatoid arthritis, or inflammatory bowel disease. Additionally, all participants were required to be willing to provide informed consent for participation in the study. The exclusion criteria included participants who had used antibiotics within the past 30 days, those with active malignancies, individuals with known immune compromised conditions, and women who were pregnant or lactating.

Data Collection

Participants were first briefed about the study, and written informed consent was obtained. Demographic and clinical data, including age, gender, medical history, oral hygiene practices, smoking status, and dietary habits, were recorded using a structured questionnaire. A detailed oral examination was then conducted by dental professionals to assess clinical indicators of dysbiosis, such as gingival inflammation, bleeding on probing, plaque index, and periodontal pocket depth. Unstimulated saliva samples were collected in sterile containers in the morning after the participants had fasted for at least two hours. Simultaneously, blood samples were obtained through venipuncture for the measurement of systemic inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).

Microbiological Analysis

Saliva samples were processed for 16S rRNA gene sequencing using next-generation sequencing (NGS) technology to analyze the composition and diversity of the oral microbiota. Sequencing data were subjected to bioinformatics analysis for bacterial identification, relative abundance profiling, and dysbiosis index calculation. Microbial signatures were then correlated with the levels of systemic inflammatory markers.

Statistical Analysis

All data were analyzed using IBM SPSS version 25.0. Descriptive statistics were used to summarize the demographic and clinical features. Chi-square tests were applied to evaluate categorical variables, while independent t-tests or Mann-Whitney U tests (depending on normality) were used for continuous data. Pearson or Spearman correlation coefficients were calculated to assess associations between microbial diversity and inflammatory markers. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of institute. All participants provided written informed consent. Participant confidentiality and data protection were maintained throughout the study in accordance with ethical research standards

Results

A total of 126 patients were included in the final analysis, with a mean age of 47.2 ± 12.6 years and a male-to-female ratio of 1:1.1 (60 males, 66 females). Among the participants, 42 (33.3%) were diagnosed with type 2 diabetes mellitus, 31 (24.6%) with cardiovascular disease, 27 (21.4%) with rheumatoid arthritis, and 26 (20.6%) with inflammatory bowel disease (IBD). The majority of patients (58.7%) had poor oral hygiene, and 64.3% had a plaque index of ≥2. Gingival bleeding was observed in 69.8% of the participants, and 38.9% had periodontal pockets deeper than 4 mm. These characteristics highlight the prevalent oral health issues among the study population, which may contribute to the observed associations with systemic inflammation. The baseline demographic and clinical characteristics of the study participants are presented in table 1.

Table 1: Baseline Demographic and Clinical Features of Study Participants (n = 126)

Variable		Mean ± SD / n (%)
Age (years)		47.2 ± 12.6
Gender	Male	60 (47.6%)
	Female	66 (52.4%)
Smoking Status (Yes)		38 (30.2%)
Poor Oral Hygiene		74 (58.7%)
Plaque Index ≥2		81 (64.3%)
Gingival Bleeding		88 (69.8%)
Periodontal Pockets >4 mm		49 (38.9%)

Oral dysbiosis, defined by a microbial dysbiosis index ≥2, was detected in 77 participants (61.1%). Among these, the most frequently co-existing condition was type 2 diabetes mellitus (35.1%), followed by cardiovascular disease (28.6%). Figure 1 shows the distribution of chronic diseases among participants with and without oral dysbiosis. While

no statistically significant associations were observed ($p > 0.05$), a higher prevalence of inflammatory bowel disease was noted in the non-dysbiosis group (28.6% vs. 15.6%), suggesting the possibility of protective microbial traits in the absence of oral dysbiosis. These findings underscore the complex relationship between oral microbial health and chronic diseases, warranting further investigation into the microbial factors that may influence systemic inflammation.

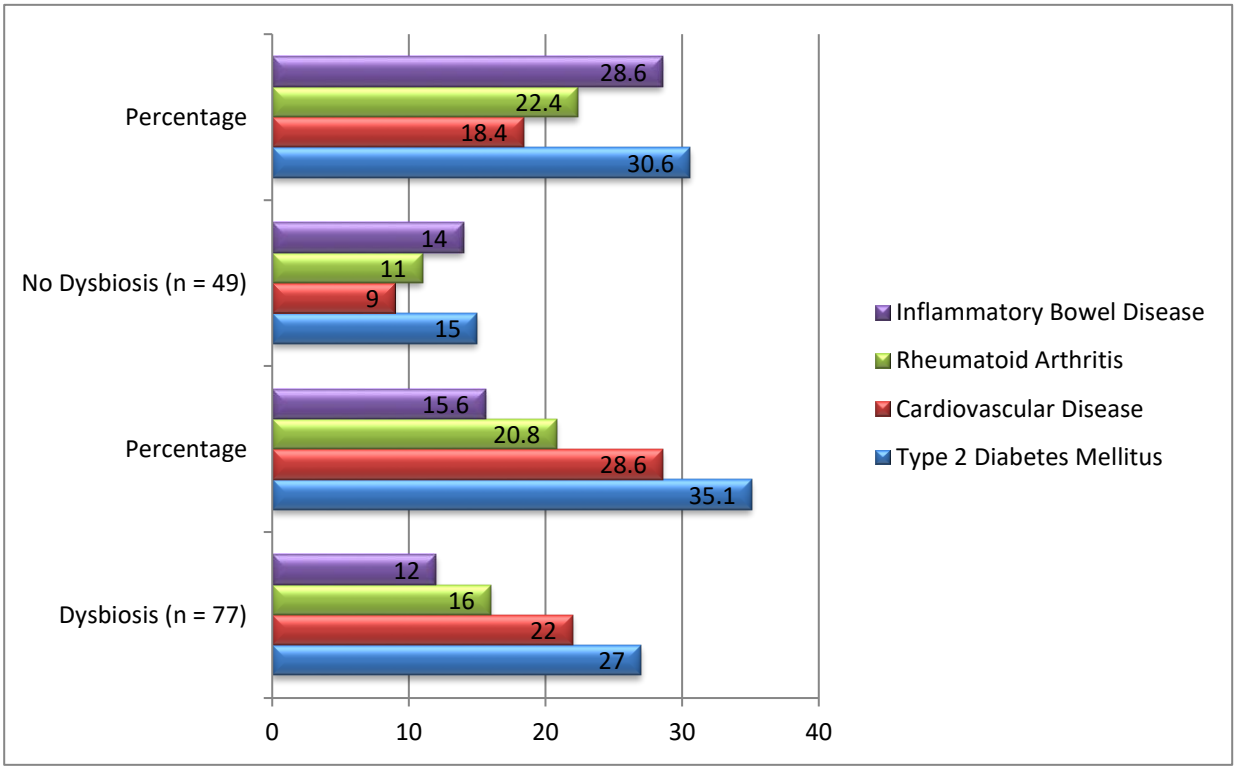

Figure 1: Distribution of Chronic Diseases among Participants With and Without Oral Dysbiosis

Inflammatory markers were significantly elevated in patients with oral dysbiosis. The mean hs-CRP level was 6.1 ± 2.8 mg/L in the dysbiosis group, compared to 3.4 ± 1.9 mg/L in the non-dysbiosis group ($p < 0.001$). Similar statistically significant differences were observed for IL-6 and TNF-α levels, with mean IL-6 levels of 18.7 ± 6.3 pg/mL in the dysbiosis group versus 12.5 ± 5.7 pg/mL in the non-dysbiosis group ($p < 0.001$), and mean TNF-α levels of 22.1 ± 5.4 pg/mL versus 16.8 ± 4.3 pg/mL, respectively ($p < 0.001$). Table 2 presents these findings, highlighting a strong association between oral dysbiosis and heightened systemic inflammation, which underscores the potential role of oral microbial imbalances in driving chronic inflammatory conditions.

Table 2: Inflammatory Markers in Patients With and Without Oral Dysbiosis

Marker	Dysbiosis (Mean ± SD)	No Dysbiosis (Mean ± SD)	p-value (t-test)
hs-CRP (mg/L)	6.1 ± 2.8	3.4 ± 1.9	<0.001
IL-6 (pg/mL)	18.7 ± 6.3	12.5 ± 5.7	<0.001
TNF-α (pg/mL)	22.1 ± 5.4	16.8 ± 4.3	<0.001

To further examine the relationship between oral microbiota and inflammation, Pearson's correlation analysis was conducted between the Shannon diversity index and systemic inflammatory markers. A moderate inverse correlation was observed for all markers, with lower Shannon indices correlating with higher levels of hs-CRP ($r = -0.52$, $p < 0.001$), IL-6 ($r = -0.46$, $p < 0.001$), and TNF-α ($r = -0.49$, $p < 0.001$). These findings support the hypothesis that reduced oral microbial diversity contributes to systemic

inflammation. When all markers were combined into a standardized inflammatory score, the correlation remained significant ($r = -0.51$, $p < 0.001$). Subgroup analysis revealed that this inverse relationship was strongest in diabetic and inflammatory bowel disease (IBD) patients, suggesting disease-specific interactions along the gut-oral-inflammatory axis. As shown in table 3.

Table 3: Correlation between Shannon Microbial Diversity Index and Systemic Inflammatory Markers

Inflammatory Marker	Mean Value (n = 126)	Shannon Index Range	Pearson Correlation (r)	p-value	Interpretation
hs-CRP (mg/L)	5.1 ± 2.9	1.4 to 3.8	-0.52	<0.001	Moderate inverse correlation
Interleukin-6 (pg/mL)	16.1 ± 6.5	1.4 to 3.8	-0.46	<0.001	Moderate inverse correlation
TNF-α (pg/mL)	19.8 ± 5.9	1.4 to 3.8	-0.49	<0.001	Moderate inverse correlation
Combined Inflammatory Score	40.5 ± 9.1	1.4 to 3.8	-0.51	<0.001	Moderate inverse correlation

Significant associations were observed between oral health factors and oral dysbiosis. Among patients with poor oral hygiene, 63 out of 74 (85.1%) had dysbiosis, compared to only 11 out of 52 (21.2%) among those with good oral hygiene ($p < 0.001$). Similar trends were observed for the plaque index and gingival bleeding. Specifically, 67 out of 77 participants (87.0%) with dysbiosis had a plaque index ≥2, compared to 14 out of 49 (28.6%) in the non-dysbiosis group ($p < 0.001$). Additionally, 69 out of 77 participants (89.6%) with dysbiosis exhibited gingival bleeding, compared to 19 out of 49 (38.8%) without dysbiosis ($p < 0.001$). The presence of periodontal pockets greater than 4 mm was also significantly associated with dysbiosis, with 37 out of 77 (48.1%) in the dysbiosis group showing this condition compared to 12 out of 49 (24.5%) in the non-dysbiosis group ($p = 0.009$). figure 2 presents these associations, reinforcing the critical link between oral hygiene and the presence of oral dysbiosis.

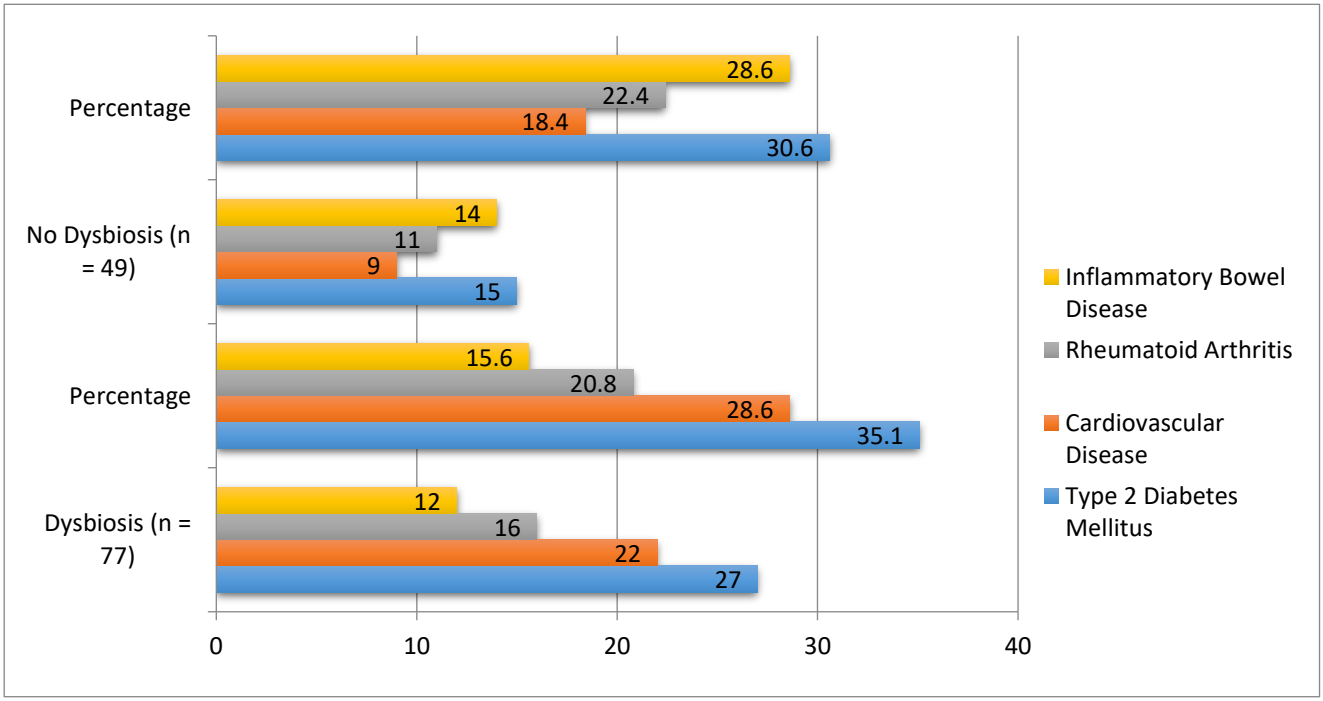

Figure 2: Oral Health Factors Associated With Oral Dysbiosis

Discussion

This study highlights a significant relationship between oral dysbiosis and systemic inflammation, suggesting that alterations in the oral microbiome may contribute to the pathogenesis of chronic diseases such as type 2 diabetes, cardiovascular disease, rheumatoid arthritis, and inflammatory bowel disease. More than 60% of participants exhibited oral dysbiosis, which was strongly associated with elevated levels of systemic inflammatory markers including hs-CRP, IL-6, and TNF-α. Additionally, a moderate inverse correlation between oral microbial diversity and inflammatory biomarkers was observed. Poor oral hygiene, high plaque index, and gingival bleeding were significant predictors of dysbiosis.

These findings are consistent with growing evidence that links the oral microbiome with systemic immune responses. Research has shown that disruptions in oral microbial balance can lead to increased mucosal permeability, bacterial translocation, and immune dysregulation all of which contribute to systemic inflammation [13]. The significant elevation in hs-CRP and cytokines in patients with dysbiosis observed in this study aligns with previous observations that chronic low-grade inflammation originating in the oral cavity can exacerbate systemic inflammatory processes [14]. Moreover, the inverse correlation between microbial diversity and inflammatory biomarkers supports the hypothesis that reduced oral microbiota diversity compromises mucosal immunity and barrier function [15].

In terms of disease-specific outcomes, our results correspond with earlier studies suggesting that periodontal pathogens play a role in insulin resistance and vascular dysfunction [16]. Patients with diabetes and cardiovascular disease in our study exhibited significantly higher levels of inflammation when oral dysbiosis was present [17]. This mirrors literature that has described oral inflammation as a contributor to glycemic dysregulation and endothelial injury [18]. The association between oral dysbiosis and rheumatoid arthritis found in our results also parallels microbiological models suggesting that certain oral bacteria may promote autoimmune responses [19]. Interestingly, although inflammatory bowel disease was not significantly associated with dysbiosis in our results, other literature indicates a potential feedback mechanism between oral and gut microbiota that merits further exploration [20].

A novel aspect of this study is the use of the Shannon diversity index as a quantitative measure of oral microbiome diversity and its significant correlation with systemic inflammation [21]. While previous studies have employed qualitative assessments or focused on single bacterial species, our approach provides a broader understanding of microbial ecology and its clinical relevance [22].

Limitations and Future Suggestions

This study had several limitations. First, it was conducted at a single center, which may limit the generalizability of the findings. Second, the cross-sectional design restricts causal inferences; while associations were found, it remains unclear whether oral dysbiosis is a cause or consequence of systemic inflammation. Third, we did not perform 16S rRNA sequencing, which could have provided species-level microbial identification. Lastly, dietary factors and medication use, which can influence both the oral microbiome and systemic inflammation, were not fully controlled. Future studies should incorporate multi-center longitudinal designs to assess causal pathways. Advanced microbial sequencing and metagenomic analyses are recommended to identify key bacterial species and functional genes involved in the gut-oral-inflammatory axis.

Conclusion

This study provides compelling evidence that oral dysbiosis is significantly associated with elevated systemic inflammation and may play a contributory role in the development and progression of chronic diseases. The observed correlations between poor oral microbial diversity and higher levels of inflammatory markers underscore the importance of maintaining oral health as a potential strategy to mitigate systemic inflammation. These findings highlight the clinical relevance of the gut-oral axis and support the need for integrated approaches that address oral microbiota in the prevention and management of chronic inflammatory conditions.

Conflict of interest

The authors declared no conflict of interest.

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