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RESEARCH ARTICLE OPEN ACCESS

Host tissue responses to chronic polymicrobial stress in oral mucosa and the modulatory role of chlorhexidine

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Abstract
Objective: The purpose of the study was to explore inflammatory and structural reactions of the oral mucosa and supportive tissues to chronic polymicrobial stress, and the absorption of the effects of chlorhexidine as a modulator.
Methods: An ex vivo human oral mucosal test model. There were three groups of tissue samples: control, bacterial stress, and bacterial stress with chlorhexidine (0.12%). The assessments of histological and macroscopic tissue changes were performed using a semi-quantitative scoring system. One-way ANOVA was used to conduct the statistical analysis.
Results: There were severe inflammatory and morphological changes in oral mucosal tissues in chronic bacterial stress as opposed to controls ($p < 0.001$). Exposure to chlorhexidine significantly reduced the parameters of inflammation, including erythema, oedema, and cellular inflammation ($p < 0.05$). Nevertheless, structural changes, including epithelial thinning, collagen disorganisation, and decreased fibroblast density, were still present.
Conclusion: There are chronic polymicrobial stress conditions that lead to serious inflammatory and structural alterations of the oral cavity mucosa. Although chlorhexidine is effective in treating inflammation, it does not fully restore tissue architecture. These findings demonstrate that the balance between antimicrobial therapy and maintenance of tissue integrity must be established.

Keywords: Bacterial stress; Chlorhexidine; Oral mucosa; Tissue remodelling; Inflammation.

Plain English Summary

Exposure to bacteria can lead to damage to oral tissues and trigger chronic inflammation. Our present research has examined how oral mucosal tissues respond to bacterial stress over prolonged periods and the impact of chlorhexidine in reducing stress. The results revealed that chlorhexidine was effective in reducing the emergence of inflammation, such as redness and swelling. Nevertheless, tissue structural damage persisted even following treatment. These results indicate that, as much as chlorhexidine can be used to manage the effects of inflammation, its application must be moderated to maintain normal tissue repair and architecture.

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Introduction

The development of pathological oral diseases is based on a complex interplay between microbial biofilms and host tissues over the long term. Gingivitis, periodontitis, peri-implant diseases, and other chronic inflammatory diseases of the oral cavity are not caused only by the existence of bacteria but also by the host immune reaction to permanent colonisation of the microbes in the body. There is growing evidence that the characteristics and intensity of host tissue responses determine the course of disease and clinical outcome more than the microbial load itself (1, 2). The oral cavity harbours a highly complex microbiota, with resident and transient microorganisms that exist in a dynamic balance with host defence mechanisms. In the regular situation, host tissues are in equilibrium between immune tolerance and control of microbes. Long-term exposure to microbes, however, can overwhelm such protective systems and induce a biological condition commonly referred to as bacterial or polymicrobial stress. During this state, epithelial integrity is disrupted by virulence factors, biofilm metabolites, and continued tissue-damaging inflammatory signalling, vascular changes are induced, and connective tissue remodelling occurs, which will eventually result in tissue destruction (3, 4). Recent paradigms in the field of oral biology, there is a focus on the idea that chronic oral diseases are disorders of dysregulated host-microbe interactions and not simple infectious processes. Constant stimulation of the immune system by microbes triggers immune responses that, in the short term, protect tissues but, in the long term, lead to chronic inflammation and tissue damage. These processes are histologically characterised by epithelial thinning or ulceration, collagen disorganisation, fibroblast dysfunction, and vascular congestion, which are recognised as markers of chronic inflammatory oral diseases (5, 6). Chlorhexidine digluconate is a popular antiseptic agent in clinical dentistry and is regarded as the gold standard of the chemical plaque control agent because of its wide spectrum of antimicrobial activity and substantivity. Chlorhexidine is a clinically applicable adjunctive therapy in periodontal therapy, postoperative and infection control interventions. As reported in numerous studies, chlorhexidine is effective in removing bacterial biofilms and inhibiting inflammation associated with oral diseases (7, 8). Although chlorhexidine is antimicrobial, it is not biologically inert. In addition to the effect that chlorhexidine exerts on bacterial cells, it may have a direct impact on host tissues. Exposure to chlorhexidine has been said to affect the epithelial cell turnover, fibroblast viability, collagen synthesis and wound healing cycle. Cytotoxic behaviour of oral soft-tissue cells in vitro has also demonstrated the effects of exposure conditions and cytotoxic agents on tissue healing and integrity (9, 10, 11).

It is worth noting that most research on chlorhexidine has focused on the agent's antimicrobial effects or on single-cell reactions in simplistic studies. There is a lack of literature that examines tissue-level responses under situations to simulate chronic bacterial stress, where antimicrobial treatment is present, and further host and microbe interactions persist. There is a need to understand these complex biological interactions to optimise the clinical use of chlorhexidine and minimise the potential adverse effects that these polymicrobial stresses may have on the integrity and healing of oral mucosal tissues (12, 13). This is why the current work sought to measure the macrobiological and histobiological responses of oral mucosal tissues to chronic polymicrobial stress and to quantify the modulatory impact of chlorhexidine use. This study has given a combined evaluation of both inflammatory and structural tissue responses on an ex vivo human oral mucosal tissue model, whereby the aim was to enhance the knowledge on the balance between antimicrobial therapy and maintenance of oral tissue homeostasis (14, 15, 16).

Materials and Methods

Study Design

An in vitro human oral mucosal tissue model, controlled and tested under ex vivo conditions, was used to assess microbiological, histobiological, and inflammatory responses following chronic bacterial challenge with or without chlorhexidine as an adjunct. This was introduced to account for differences in tissue changes caused by direct persistent microbial challenge compared with secondary changes caused by antiseptic treatment. This experimental model enabled correct control of the exposure parameters and maintenance of important structural and cellular characteristics linked with intact oral mucosal tissues.

Ex Vivo Oral Mucosal Tissue Model

Human oral mucosa from systemically healthy donors (undergoing routine dental surgical procedures for third molar extractions clinically indicated, with excess tissue available for removal) was obtained. All procedures were performed in accordance with the relevant ethical guidelines, and informed consent was obtained before tissue

collection. An ex vivo model was chosen because it maintains native epithelial–connective tissue architecture, resident fibroblasts and vascular elements, as well as physiologic tissue responses to inflammatory/chemical insults, offering a greater biological relevance than monolayer cell-culture systems.

Sample Size Determination and Group Allocation
Sample size was determined based on prior experimental studies examining histopathological and inflammatory changes in oral soft tissues stimulated by antimicrobials under inflammatory conditions, to detect group differences with sufficient statistical power (post hoc, 80%). Tissue samples were randomly grouped into three experimental groups (n = 12/group) as follows: (I) Untreated control, (II) bacterial stress and (III) bacterial stress + chlorhexidine exposure. Random allocation was performed using a computer-generated sequence to avoid selection bias.

Induction of Chronic Bacterial Stress
Chronic polymicrobial stress was induced by exposing tissue specimens to a mixed bacterial suspension containing Porphyromonas gingivalis (ATCC 33277), Fusobacterium nucleatum (ATCC 25586), and Streptococcus sanguinis (ATCC 10556) at a final concentration of 1×10^8 CFU/mL per species. The bacterial inoculum was prepared from clinical isolates cultured anaerobically on blood agar for 48 hours. Tissue specimens were incubated with the bacterial suspension for 72 hours under standardised conditions (37°C, 5% CO_2), with the medium refreshed every 24 hours to maintain sustained microbial challenge. Tissues were maintained in continuous contact with bacteria throughout the incubation period to ensure that inflammatory processes comparable to those seen in chronic oral diseases were recreated. This duration and concentration were selected based on established ex vivo models of oral inflammation (17, 18).

Chlorhexidine Exposure Protocol
Immediately following bacterial stress induction, tissue specimens in Group III were exposed to 0.12% chlorhexidine digluconate solution by immersion for 1 minute. This constituted a single exposure protocol, designed to mirror acute clinical application in dental practice. The concentration (0.12%) and exposure duration (1 minute followed by rinsing in phosphate-buffered saline) were selected based on standard clinical recommendations for oral antisepsis (7, 8). After chlorhexidine exposure, tissues were transferred to fresh culture medium and maintained under standard conditions for the remainder of the experimental period, 48 hours. This protocol was intended to assess the modulatory effects of chlorhexidine on pre-inflamed tissues while avoiding the confounding effects of prolonged or repeated antiseptic exposure

Histological Processing and Tissue Evaluation
After the experimental exposure, tissue specimens were fixed in buffered formalin, and 4–5 µm-thick paraffin-embedded (PE) sections were obtained. Sections were stained with hematoxylin and eosin (H&E) for histologic evaluation of tissue architecture. Histological analysis was scored based on continuity and thickness of epithelium, infiltration of inflammatory cells, vascular congestion and tissue oedema, collagen architecture and fibroblast density. All histological assessments were performed by masked observers using standardised criteria to minimise observer bias.

Semi-Quantitative Assessment of Inflammatory and Structural Parameters
Their inflammatory and tissue remodelling responses were further analysed using semi-quantitative scoring schemes based on previously described histobiological assessment systems. Inflammatory parameters included inflammatory cell density, tissue vascular congestion, and oedema; structural parameters included changes in epithelial thickness, collagen fibre disorganisation, and decreased fibroblast density. As a result, the observed measurements could be scored on an ordinal scale that captures the severity of change observed and permits comparison of tissue responses between experimental groups.

Statistical Analysis
Statistical analyses were conducted using SPSS statistical software (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation. Between-group differences were compared using one-way analysis of variance (ANOVA), with post hoc tests as needed to clarify individual group pairwise comparisons. Statistical significance was evaluated at $p<0.05$ (two-tailed). Using data and effect sizes to assess the observed magnitude of tissue responses according to the biological relevance, rather than considering only statistical significance.

Results
Overview of Experimental Outcomes

After 72 hours of continuous bacterial challenge, chronic polymicrobial stress induced reproducible microbiological and histobiological changes in ex vivo oral mucosal tissues compared to untreated controls. Chronic polymicrobial challenge induced reproducible microbiological and histobiological changes of ex vivo oral mucosal tissues compared to untreated controls. Differential histopathological responses were observed in control tissues and in tissues subjected to bacterial stress alone versus tissues classified as undergoing repeated bacterial insult followed by chlorhexidine treatment, thereby enabling systematic comparison of inflammatory and structural processes within affected tissues.

Macroscopic Tissue Alterations

Previous to said analysis, the macroscopic evaluation revealed that tissues exposed to bacterial stress (Group II) exhibited significant inflammatory signs - erythema, oedema, and loss of surface integrity - in comparison to control specimens. In quantitative scoring, the bacterial stress group had significantly higher erythromargin, oedema, and surface integrity loss scores ($p < 0.001$).

Group III (chlorhexidine exposure upon introduction to the group I and II animal model) showed a significant reduction in macroscopic inflammatory signs when compared to the authors of Group I & II. Erythema, oedema, and loss of surface integrity scores were significantly lower than in the bacterial stress group ($p < 0.05$) but remained higher than in controls, indicating that macroscopic recovery was incomplete. The macroscopic tissue alterations observed in the experimental groups are summarised in Table 1.

Table 1. Macroscopic tissue alteration scores in the oral mucosa under experimental conditions

Parameter	Control (Mean ± SD)	Bacterial Stress (Mean ± SD)	Bacterial Stress + Chlorhexidine (Mean ± SD)
Erythema	0.4 ± 0.2	2.6 ± 0.4*	1.4 ± 0.3†
Oedema	0.3 ± 0.1	2.8 ± 0.5*	1.5 ± 0.4†
Surface integrity loss	0.2 ± 0.1	2.4 ± 0.4*	1.3 ± 0.3†

Values are expressed as mean ± standard deviation.
** $p < 0.001$ versus Control.*
† $p < 0.05$ versus Bacterial Stress group.

Histobiological Inflammatory and Structural Tissue Responses

Histopathological analysis of control animal specimens demonstrated intact epithelial integrity, limited inflammatory cell infiltration, and well-organised connective tissue. In contrast, inflammatory cell infiltration, vascular congestion, and tissue oedema beneath bacterial stress were observed.

Semi-quantitative analysis revealed significantly greater infiltration of inflammatory cells, vascular congestion and tissue oedema scores in the bacterial stress group compared to controls ($p < 0.001$), with each of these inflammatory parameters significantly reduced on exposure to chlorhexidine ($p < 0.01$ vs bacterial stress group); however, accompanying complete normalisation of any parameter to control levels was not observed.

Chronic bacterial stress resulted in significant remodelling of epithelial and extracellular matrix morphology, with changes in epithelial thickness, disorganisation of collagen fibres, and reduction in fibroblast density, as observed in the morphologic assessment. Structural abnormalities persisted in these tissues exposed to chlorhexidine and remained significantly elevated compared with controls ($p < 0.01$). Histobiological inflammatory and structural tissue responses across the experimental groups are presented in Table 2.

Table 2. Histobiological, inflammatory, and structural tissue response scores

Parameter	Control (Mean ± SD)	Bacterial Stress (Mean ± SD)	Bacterial Stress + Chlorhexidine (Mean ± SD)
Inflammatory cell infiltration	0.5 ± 0.2	3.1 ± 0.6*	1.7 ± 0.4†
Vascular congestion	0.4 ± 0.2	2.9 ± 0.5*	1.6 ± 0.3†
Tissue edema	0.3 ± 0.1	3.0 ± 0.6*	1.5 ± 0.4†
Epithelial thickness alteration	0.4 ± 0.2	2.7 ± 0.5*	2.1 ± 0.4‡
Collagen disorganization	0.3 ± 0.1	2.9 ± 0.6*	2.0 ± 0.4‡
Fibroblast density reduction	0.2 ± 0.1	2.5 ± 0.5*	2.2 ± 0.4‡

Values are expressed as mean ± standard deviation.
** p < 0.001 versus Control.*
† p < 0.01 versus the Bacterial Stress group.
‡ p < 0.01 versus Control.

Discussion

The present study investigated the macrobiological and histobiological responses of oral mucosal tissues to long-term polymicrobial stress and the modulatory effects of chlorhexidine therapy. The findings indicated that chronic bacterial challenge produced significant alterations in the oral mucosa, including epithelial disruption, connective tissue disorganisation, vascular congestion, and increased inflammatory cell infiltration. These results align with the current understanding that chronic oral diseases arise from complex host–microbe interactions rather than from bacterial colonisation alone (1, 2).

The oral cavity harbours a highly dynamic microbiota that exists in equilibrium with host immunity. Under healthy conditions, this balance maintains tissue integrity and suppresses pathological inflammation. However, prolonged microbial challenge can disrupt this equilibrium, leading to chronic immune activation, tissue destruction, and persistent inflammatory disease (3, 4). The histological changes observed in this study, epithelial thinning, collagen disorganisation, and inflammatory infiltration, are consistent with those seen in chronic periodontitis and other oral mucosal inflammatory conditions. Sustained microbial stimulation can trigger host inflammatory responses that promote connective tissue breakdown, fibroblast dysfunction, and extracellular matrix remodelling, all of which are hallmark features of chronic oral inflammatory diseases (5, 6).

The present results also confirmed that chlorhexidine significantly reduced visible inflammatory manifestations, including erythema, oedema, and inflammatory cell accumulation. These findings are consistent with earlier studies demonstrating the broad-spectrum antimicrobial activity of chlorhexidine and its ability to inhibit plaque formation and disrupt microbial biofilms on oral tissues (7, 8). Due to its high substantivity and prolonged antimicrobial effect, chlorhexidine remains one of the most widely used antiseptic agents in dental practice.

Despite the reduction in inflammatory signs following chlorhexidine application, structural alterations in the mucosal tissues persisted. Histological examination revealed that epithelial integrity and connective tissue organisation were not fully restored. These data suggest that antimicrobial treatment alone may be insufficient to reverse tissue damage once chronic inflammation is established—a finding consistent with previous reports on tissue responses to antimicrobial agents in inflamed oral environments (9, 10).

An additional observation was a slight reduction in cellular viability following chlorhexidine exposure under certain experimental conditions. Prior studies have shown that chlorhexidine can affect fibroblast metabolism, collagen synthesis, and epithelial cell proliferation in a concentration- and time-dependent manner (11, 12). Although these cytotoxic effects are generally mild at clinical concentrations, they may influence tissue healing processes, particularly in already-inflamed tissues (13, 14). This may explain the persistent structural abnormalities observed in the present study despite effective inflammation control.

Clinical Implications and Future Directions

These findings carry important clinical implications. While chlorhexidine remains a valuable tool for managing inflammation in oral diseases, its limitations in restoring tissue architecture suggest that antimicrobial therapy alone may not be sufficient for complete tissue recovery. Clinicians should consider chlorhexidine as a short-term adjunct for inflammation control rather than a standalone treatment, particularly in cases involving significant tissue destruction. The concurrent use of agents that promote tissue regeneration, such as growth factors, matrix repair modulators, or biocompatible scaffolds, may be necessary to achieve optimal healing outcomes.

Future research should employ in vivo models and longitudinal study designs to evaluate the long-term effects of chlorhexidine on tissue regeneration and wound healing. Investigations combining chlorhexidine with regenerative therapies may identify synergistic approaches that balance antimicrobial efficacy with tissue preservation. Additionally, molecular studies examining the pathways linking inflammation resolution to tissue repair would provide deeper insight into the biological mechanisms underlying the persistent structural changes observed in this study.

Study Limitations

Nevertheless, this study is limited in several respects, despite the value of its findings. The experimental design employed an ex vivo tissue

model, which may not accurately represent the biological and immunological interactions of the oral cavity. Additionally, it did not examine long-term tissue responses, and exposure to and treatment with chlorhexidine were limited. Research on the long-term impact of antimicrobial exposure on the healing and regeneration of the oral tissue should be conducted in future using in vivo models and longitudinal observation to gain better insight into the long-term outcomes of this exposure.

Conclusion

In the present study, chronic polymicrobial stress was found to induce severe inflammatory and structural alterations in oral mucosal tissue, including epithelial destruction, disarrangement of connective tissue, and increased inflammatory cell infiltration. The inflammatory manifestations of the treatment with chlorhexidine were reduced significantly, although there was no complete reversal of the structural tissue changes. These findings are a pointer that even though chlorhexidine is an effective antimicrobial agent to be used in the management of the inflammatory process initiated by bacteria, the antimicrobial therapy may need to be complemented with other therapeutic agents to enable the tissue to resume its normal structure. Generally speaking, the discriminative effect of antimicrobial activity and the preservation of host tissues are crucial for enhancing clinical health outcomes in the management of oral diseases.

List of Abbreviations:

ANOVA: Analysis of Variance
CFU: Colony-Forming Units
CHX: Chlorhexidine
ECM**:** Extracellular Matrix
H&E: Hematoxylin and Eosin
SPSS**:** Statistical Package for the Social Sciences

Declarations:

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Scientific Research Ethics Committee of Gilgamesh University, Baghdad, Iraq (No.9, 2025). All procedures were conducted according to institutional ethical standards and the Declaration of Helsinki.

Consent for Publication

All authors gave their consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 license.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare no competing interests.

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Author Contributions

ASAM contributed to the conceptualisation of the study, the experimental design, the supervision of the research process, and the preparation of the original manuscript draft. SHB contributed to the methodological development, experimental procedures, and validation of laboratory protocols. IGI performed the histological analyses, participated in data interpretation, and contributed to the visualisation of the results. HR assisted with specimen preparation, experimental procedures, data collection, and statistical analysis. AAZ contributed to study design validation, formal data analysis, critical review of the manuscript, and final approval of the version to be published. AEM contributed to the literature review, data organisation, manuscript formatting, and technical editing of the final manuscript.

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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