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Space dentistry: Oral biofilm, periodontal health, and integrated future protocols as a global reference

Odontologia espacial: Biofilme oral, saúde periodontal e protocolos futuros integrados como referência global

Odontología espacial: Biopelícula oral, salud periodontal y protocolos futuros integrados como referencia global

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Abstract
Objective: To establish a comprehensive reference on oral biofilm and periodontal health in microgravity, addressing existing knowledge gaps, proposing innovative protocols, and preventive strategies for prolonged space missions. Methods: Narrative review of international literature, integrating clinical data, microgravity experiments, in vitro/in vivo modeling, and computational simulations (Hall-Stoodley et al., 2004; Lewandowski, 2000; Vélez Justiniano et al., 2023). Results: Microgravity alters the composition of the oral microbiome, promotes resistant biofilms, and compromises local immunity (Salido et al., 2025; Koenig & Pierson, 1997). Current protocols partially reduce superficial biofilm but fail to address subgingival biofilm, longitudinal monitoring, and personalized oral hygiene. Innovative strategies include metagenomic sequencing (Srinivasan et al., 2021), tele-dentistry, antimicrobial surfaces, bacteriophage therapies, regenerative scaffolds, and AI for continuous monitoring. Identified gaps have been addressed, suggesting detailed methodologies for future research. Conclusion: Space dentistry emerges as a critical field in light of the challenges that microgravity imposes on the oral microbiome and astronauts' periodontal health. This review demonstrates that changes in subgingival biofilm, antimicrobial resistance, and local immunosuppression require protocols beyond traditional strategies. Therefore, an integrative model is proposed that employs multi-omics analyses, 3D modeling, bioactive surfaces, personalized immune modulation, and remote monitoring through artificial intelligence and tele-dentistry. By integrating prevention, diagnosis, and advanced therapies into a comprehensive plan, this research scientifically and technologically supports the maintenance of oral health in prolonged space missions, aiding in the development of global and standardized guidelines for space dentistry.
Keywords: Microgravity; Oral biofilm; Periodontal health; Astronauts; Space dentistry; Antimicrobial resistance; Innovative protocols.

Resumo
Objetivo: Estabelecer uma referência abrangente sobre biofilme oral e saúde periodontal em microgravidade, abordando lacunas de conhecimento existentes, propondo protocolos inovadores e estratégias preventivas para missões espaciais prolongadas. Métodos: Revisão narrativa da literatura internacional, integrando dados clínicos, experimentos em microgravidade, modelagem in vitro/in vivo e simulações computacionais (Hall-Stoodley et al., 2004; Lewandowski, 2000; Vélez Justiniano et al., 2023). Resultados: A microgravidade altera a composição do microbioma oral, promove biofilmes resistentes e compromete a imunidade local (Salido et al., 2025; Koenig & Pierson, 1997). Os protocolos atuais reduzem parcialmente o biofilme superficial, mas não abordam o biofilme subgengival, o monitoramento longitudinal nem a higiene oral personalizada. Estratégias inovadoras incluem sequenciamento metagenômico (Srinivasan et al., 2021), teleodontologia, superfícies antimicrobianas, terapias com bacteriófagos, scaffolds regenerativos e uso de inteligência artificial para monitoramento contínuo. As lacunas identificadas foram tratadas, sugerindo metodologias detalhadas para pesquisas futuras. Conclusão: A odontologia espacial surge como um campo crítico frente aos desafios impostos pela microgravidade ao microbioma oral e à saúde periodontal dos astronautas. Esta revisão demonstra que alterações no biofilme subgengival, resistência antimicrobiana e imunossupressão local exigem protocolos além das estratégias tradicionais. Assim, propõe-se um

modelo integrativo que utiliza análises multiômicas, modelagem 3D, superfícies bioativas, modulação imunológica personalizada e monitoramento remoto por inteligência artificial e teleodontologia. Ao integrar prevenção, diagnóstico e terapias avançadas em um plano abrangente, esta pesquisa apoia cientificamente e tecnologicamente a manutenção da saúde oral em missões espaciais prolongadas, contribuindo para o desenvolvimento de diretrizes globais e padronizadas para a odontologia espacial.
Palavras-chave: Microgravidade; Biofilme oral; Saúde periodontal; Astronautas; Odontologia espacial; Resistência antimicrobiana; Protocolos inovadores.

Resumen
Objetivo: Establecer una referencia integral sobre el biofilm oral y la salud periodontal en microgravedad, abordando las lagunas de conocimiento existentes, proponiendo protocolos innovadores y estrategias preventivas para misiones espaciales prolongadas. Métodos: Revisión narrativa de la literatura internacional, integrando datos clínicos, experimentos en microgravedad, modelado in vitro/in vivo y simulaciones computacionales (Hall-Stoodley et al., 2004; Lewandowski, 2000; Vélez Justiniano et al., 2023). Resultados: La microgravedad altera la composición del microbioma oral, favorece biofilms resistentes y compromete la inmunidad local (Salido et al., 2025; Koenig & Pierson, 1997). Los protocolos actuales reducen parcialmente el biofilm superficial, pero no abordan el biofilm subgingival, el monitoreo longitudinal ni la higiene oral personalizada. Las estrategias innovadoras incluyen secuenciación metagenómica (Srinivasan et al., 2021), teleodontología, superficies antimicrobianas, terapias con bacteriófagos, scaffolds regenerativos y el uso de inteligencia artificial para monitoreo continuo. Las lagunas identificadas se han abordado, sugiriendo metodologías detalladas para futuras investigaciones. Conclusión: La odontología espacial surge como un campo crítico ante los desafíos que la microgravedad impone sobre el microbioma oral y la salud periodontal de los astronautas. Esta revisión demuestra que los cambios en el biofilm subgingival, la resistencia antimicrobiana y la inmunosupresión local requieren protocolos más allá de las estrategias tradicionales. Por lo tanto, se propone un modelo integrador que utiliza análisis multi-ómicos, modelado 3D, superficies bioactivas, modulación inmunológica personalizada y monitoreo remoto mediante inteligencia artificial y teleodontología. Al integrar prevención, diagnóstico y terapias avanzadas en un plan integral, esta investigación respalda científica y tecnológicamente el mantenimiento de la salud oral en misiones espaciales prolongadas, contribuyendo al desarrollo de directrices globales y estandarizadas para la odontología espacial.
Palabras clave: Microgravedad; Biofilm oral; Salud periodontal; Astronautas; Odontología espacial; Resistencia antimicrobiana; Protocolos innovadores.

1. Introduction

Long-duration space exploration presents new challenges for human health, particularly oral health. In microgravity, oral biofilms exhibit higher bacterial density, increased EPS production (Martins et al., 2010; Srinivasan et al., 2021), and alterations in quorum sensing communication (Kievit et al., 2009; Jayaraman et al., 2008). The subgingival biofilm remains the greatest knowledge gap, being crucial for periodontitis, antimicrobial resistance, and chronic inflammation (Donlan, 2001; Nazir et al., 2019).

Moreover, transient immunosuppression in microgravity exacerbates bacterial persistence, delays gingival healing, and increases the risk of systemic complications (Crucian et al., 2018; Franklin et al., 2014). Current protocols do not address longitudinal monitoring, individualized personalization, or integration with emerging technologies such as tele-dentistry and multi-omics (Blue et al., 2023; Guzmán-Soto et al., 2021).

This article aims to establish a comprehensive reference on oral biofilm and periodontal health in microgravity, addressing existing knowledge gaps, and proposing innovative protocols and preventive strategies for long-duration space missions.

2. Methodology

A bibliographic search was conducted, of a qualitative nature and specifically of the non-systematic narrative review type. A simple search was performed on Google Scholar, which is a free and open-access database, using the following search terms: Microgravity; Oral biofilm; Periodontal health; Astronauts; Space dentistry; Antimicrobial resistance; Innovative protocols.

3. Results and Discussion

The review results demonstrate significant alterations in the oral microbiome under microgravity, antimicrobial resistance, and difficulties in periodontal healing.

Subgingival Biofilm

Understanding the dynamics of the subgingival biofilm in a microgravity environment is a new challenge in space medicine and translational dentistry. Research conducted in space missions and microgravity simulation platforms indicates that the space environment significantly alters microorganism behavior, modifying the structural and functional characteristics of oral biofilms (Nagaraja & Ramesh, 2023; Mora et al., 2022). The absence of gravity affects shear forces and salivary fluid flow, resulting in biofilm thickening, reorganization of the polymeric extracellular matrix, and increased expression of genes linked to virulence, quorum sensing, and antimicrobial resistance (Martins et al., 2010; de Kievit & Iglewski, 2009).

Under normal conditions, the subgingival biofilm has a complex stratification, containing anaerobic zones that favor the development of periodontopathogenic bacteria such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* (Socransky et al., 1998). In microgravity, there is an observed increase in bacterial density and three-dimensional reorganization, promoting the formation of compact microcolonies that hinder the action of antimicrobial agents (Kim et al., 2013). Computational modeling studies indicate that microgravity modifies nutrient diffusion and oxygen gradients, affecting bacterial metabolism and generating a more hypoxic microenvironment, comparable to that found in deep periodontal pockets (Salido et al., 2025; Wilson et al., 2021). Moreover, microgravity compromises the immune response, amplifying bacterial persistence. Reduced saliva production and secretory IgA activity impair the natural defense of the oral mucosa (Crucian et al., 2018). As a result, a cycle of chronic dysbiosis occurs, in which commensal species lose dominance and opportunistic microorganisms become predominant, increasing the risk of inflammation and periodontal attachment loss (Nazir et al., 2019; Urbaniak et al., 2020). The scientific gap lies in the absence of longitudinal experiments specifically focused on the subgingival biofilm under prolonged microgravity. Most studies are limited to saliva samples or two-dimensional models, failing to adequately reproduce the ecological complexity of the gingival sulcus (Gao et al., 2024).

Thus, the creation of three-dimensional models in biomimetic scaffolds is proposed to evaluate microbial-tissue interactions under real microgravity conditions, combining multi-omics techniques and artificial intelligence for predictive analysis (Li et al., 2023; Gupta et al., 2024).

Proposed Protocol:

- Complex longitudinal sampling: Collection of subgingival biofilm before, during, and after the mission, including multiple periodontal sites (healthy, inflamed, and with periodontal pockets >4 mm). Use standardized probes and samples stored in RNA-preserving buffer for metatranscriptomics.
- Multi-omics analysis: Metagenomics, metatranscriptomics, metaproteomics, and metabolomics to map bacterial structure, function, and virulence. Algorithms to predict antimicrobial resistance based on efflux sequences, β-lactamases, and target mutations.
- 2D/3D in vitro modeling under simulated microgravity: Use of rotating clinostats, rotary bioreactors, and real microgravity platforms such as the ISS. Biofilms grown in three-dimensional scaffolds with simulated extracellular matrix to observe growth patterns, thickness, EPS, and quorum sensing communication under controlled conditions. Machine learning applied to correlate microbial composition, local immune responses, and antimicrobial therapy impacts, creating predictive models of colonization and pathogenicity.

Antimicrobial Resistance

Antimicrobial resistance is a major global health threat and tends to intensify in isolated environments, such as the International Space Station (ISS). Studies indicate that microorganisms exposed to microgravity develop adaptive mutations conferring higher resistance to traditional antibiotics, such as β-lactams and macrolides (Jayaraman et al., 2008; Cortesão et al., 2020). These adaptations involve increased expression of efflux pumps, thickening of the cell wall, and conformational changes in target proteins (Salido et al., 2025; Zea et al., 2018). In oral biofilms, this resistance is further intensified by the polymeric extracellular matrix, which acts as a physical and chemical barrier against antimicrobial agents. Microgravity exacerbates this phenomenon by altering bacterial metabolism and inducing the expression of stress-related genes, leading to the formation of more mature and resistant biofilms (Kim et al., 2013; Huang et al., 2022).

To overcome these limitations, alternative therapies have been suggested, including adaptive bacteriophages, nanotechnology, and antimicrobial phototherapy (Han et al., 2023; Park et al., 2022). The application of bioactive surfaces and coatings containing silver, zinc, or titanium oxide nanoparticles has shown promising results in reducing bacterial adhesion and biofilm formation on dental devices and prostheses (Mokhtari et al., 2023; Dutta et al., 2021). The incorporation of AI for real-time genetic monitoring of resistance also represents a disruptive advancement. Deep learning algorithms can correlate genetic patterns with phenotypic responses, predicting the emergence of resistant strains before they reach critical clinical levels (Liu et al., 2023; Han et al., 2024).

Applied to space dentistry, this approach would allow personalized interventions based on each astronaut's individual microbiome.

Proposed Protocol:

- In vitro comparative tests: Compare traditional antibiotics (penicillins, tetracyclines, macrolides) with adaptive bacteriophages, combinatorial experiments with antimicrobial surfaces, and phototherapy. Establish specific MIC (Minimum Inhibitory Concentration) and MBEC (Minimum Biofilm Eradication Concentration) values for subgingival biofilm.
- Antimicrobial surfaces and devices: Use of nanostructures and bioactive coatings in intraoral devices, prostheses, brackets, and dental sealants, analyzing long-term effects on bacterial growth and biofilm adhesion.
- Functional resistance assays: Functional sequencing of resistance genes, β-lactamase enzymatic activity, efflux pumps, and membrane alterations. Comparison between simulated microgravity and Earth conditions to map bacterial adaptation.
- Technological integration: AI for continuous monitoring of biofilm resistance evolution, enabling early alerts and real-time adjustment of personalized antimicrobial protocols.

Oral Immunity

Oral immunity undergoes profound alterations in microgravity. NASA studies have shown a significant reduction in neutrophil phagocytic activity, decreased pro-inflammatory cytokines, and reduced expression of cell adhesion molecules (Crucian et al., 2018). This immune dysfunction results in increased susceptibility to opportunistic infections and worsening of chronic inflammatory conditions such as periodontitis (Patel et al., 2023).

The microbiome-immune-tissue axis is fundamental to this discussion. In microgravity environments, epigenetic reprogramming of immune cells occurs, affecting the production of IgA, IL-1β, IL-6, and TNF-α (Jiang et al., 2021). These changes favor the persistence of subgingival biofilm and reduce tissue repair ability (Zhang et al., 2021). Human gingival tissue culture models under simulated microgravity show decreased immune signaling and ineffective leukocyte recruitment, resulting in low-grade but persistent inflammation (Li et al., 2024). Personalized immune modulation emerges as an innovative approach to restore oral immune balance. Supplementation with vitamin D, zinc, and polyphenols has been shown to effectively recover immune responses and reduce inflammation in astronauts and simulated models (Kaur et al., 2022). The use of specific probiotics, such as *Lactobacillus reuteri* and *Bifidobacterium longum*, has also demonstrated benefits in modulating the oral microbiome and decreasing inflammatory mediators (Gupta et al., 2024).

Proposed Protocol:

- Continuous monitoring of salivary biomarkers: Levels of secretory IgA, pro- and anti-inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-10), lactoferrin, defensins, and antimicrobial peptides. Periodic sampling and automated analysis via biosensors integrated into intraoral devices.
- Advanced in vitro models: Culture of human gingival tissues with integrated immune cells in microgravity microchips or 3D scaffolds. Assess cellular recruitment, cytokine production, and biofilm interaction.
- Personalized immune modulation: Supplementation based on genetic and microbial profiles (vitamin D, polyphenols, probiotics), use of pharmacological local immune modulators, and oxidative stress control.

Gingival Healing

Tissue regeneration in space environments is a substantial challenge. The absence of gravity directly affects the activity of fibroblasts, osteoblasts, and mesenchymal stem cells, decreasing extracellular matrix production and slowing the healing process (Nazir et al., 2019; Jafari et al., 2020). In vitro assays show that cells exposed to microgravity exhibit cytoskeletal disorganization and changes in the expression of genes related to adhesion and cell proliferation (Zhang et al., 2021). The use of biocompatible scaffolds enriched with growth factors, such as VEGF, FGF, and BMP, has shown encouraging results in accelerating healing and promoting periodontal regeneration, even under simulated microgravity conditions (Jafari et al., 2020; Hamed et al., 2023). Moreover, combining 3D bioprinting techniques with AI monitoring can enable guided regeneration adjusted in real time, taking into account the tissue response of each individual (Ramesh et al., 2024).

The combination of guided regeneration, immune modulation, and biofilm control represents a synergistic and multidimensional approach to preserving periodontal integrity during long-duration space missions. This integration of tissue engineering, nanotechnology, and molecular biology establishes a new paradigm in regenerative dentistry applied to space environments (Li et al., 2023; Gao et al., 2024).

Proposed Protocol:

- Application of biocompatible regenerative scaffolds (fibrin, collagen, hydrogel matrix) (Jafari et al., 2020).
- Controlled growth factors for microgravity conditions.
- Assessment of tissue integration via high-resolution imaging and molecular markers (Zhang et al., 2021).

Longitudinal Monitoring

The lack of continuous longitudinal monitoring is one of the main limitations in current literature. Most available studies are based on single-point observations, preventing temporal correlations between microbial, immunological, and therapeutic changes (Zhou et al., 2024). In microgravity, this limitation is exacerbated, as isolation and the impossibility of early corrective interventions significantly increase the risk of complications (Ramakrishnan et al., 2023). Developing longitudinal monitoring protocols based on integrated biosensors emerges as an urgent need. Devices capable of continuously recording salivary parameters—such as pH, cytokine levels, and oxidative stress markers—could provide real-time data for personalized therapeutic adjustment (Kim et al., 2024). These systems, combined with international databases and AI algorithms, would allow predictive analyses capable of anticipating inflammatory flare-ups or severe dysbioses before progressing to clinical pathologies.

Proposed Protocol:

- Next-generation tele-dentistry: Intraoral devices connected via satellite with cameras and sensors for biofilm, saliva, and gingival pressure. Automated data collection and secure transmission to control centers.
- AI and predictive algorithms: Real-time analysis of biofilm evolution, antimicrobial resistance, inflammation, and tissue integrity. Automatic alerts to the astronaut or ground team.
- Centralized longitudinal record: Secure storage of multi-omics data, images, functional assays, and therapy responses, creating a global database for future research.

Personalized Protocols

Implementing personalized periodontal health protocols under microgravity represents an innovative and necessary frontier in contemporary space dentistry. Literature shows that standardized protocols, although effective under Earth conditions, do not account for the wide individual variability observed among astronauts and experimental populations—particularly regarding microbial composition, immune profile, and genetic susceptibility (Zhou et al., 2024; Kim et al., 2024). This gap reduces the effectiveness of oral hygiene strategies, antimicrobial therapies, and regenerative processes, making the development of adaptive, data-driven approaches essential.

The main limitation of current protocols is the absence of interindividual personalization, which overlooks the uniqueness of the oral microbiome, genetic diversity, and immunological variations among individuals exposed to microgravity (Silva et al., 2022). This lack compromises therapy effectiveness and increases the risk of progressive periodontal disorders, as inflammatory responses and microbial patterns are strongly influenced by genetic and environmental factors (Kaur et al., 2023).

Proposed Protocol:

- Adaptive oral hygiene: Creation of personalized hygiene kits composed of brushes, floss, and antimicrobial devices calibrated according to individual microbial composition and immune response detected by biosensors. These systems would integrate microcameras and sensors for pH, temperature, and gingival oxygen, automatically adjusting hygiene intensity and frequency according to the user's biological parameters (Kim et al., 2024).
- Personalized functional supplementation: Controlled administration of specific probiotics, vitamins, minerals, and targeted immune modulators based on genetic analyses and longitudinal individual data. These interventions aim to balance the microbiome and enhance immune response under oxidative and inflammatory stress induced by microgravity (Ramakrishnan et al., 2023).
- Dynamic AI adjustment: Application of artificial intelligence (AI) algorithms as a central element, allowing real-time recalibration of hygiene, antimicrobial, and tissue regeneration protocols based on continuous intraoral biosensor and saliva data. This approach enables automated feedback, creating an adaptive cycle of diagnosis, prevention, and continuous intervention (Zhang et al., 2023).

Multidisciplinary Integration

The feasibility and effectiveness of personalized protocols depend on consistent multidisciplinary integration among dentistry, molecular biology, materials engineering, space medicine, and data science (Silva et al., 2022). Recent literature emphasizes that isolating studies in specific fields limits generalization and applicability, preventing the creation of standardized international guidelines (Yamaguchi et al., 2022). The lack of coordination between disciplines and data-sharing platforms is a critical obstacle. The absence of unified global databases hinders multicenter comparisons and reduces scientific reproducibility of experiments conducted under microgravity (Zhou et al., 2024).

Proposed Protocol:

- Global data platform: Establishment of a centralized digital infrastructure with secure, interoperable access for international researchers. This platform would gather clinical, genetic, bioinformatic, and engineering data, enabling collaborative and multicenter long-term analyses (Kimura et al., 2023).
- Interdisciplinary coordination: Formation of integrated teams of dentists, immunologists, microbiologists, materials engineers, AI specialists, and space physicians. This convergence ensures cross-validation of methodologies, protocol optimization, and development of global safety standards (Smith et al., 2021).
- Development of global standards: Definition of evidence-based guidelines for maintaining periodontal health in microgravity, covering prevention, treatment, and continuous monitoring. These internationally recognized guidelines can serve as models for advanced terrestrial protocols and prolonged isolation hospital environments (Carmeliet et al., 2022).

Suggested Future Protocols

Subgingival Biofilm in 2D/3D and Microgravity

In vitro models of subgingival biofilms in 2D and 3D simulating microgravity allow understanding of structural and dynamic changes in the oral microbiome in space environments. Microgravity favors denser biofilms with altered bacterial communication and increased antimicrobial resistance, essential for developing therapeutic strategies in long missions (Nickerson et al., 2004; Kim et al., 2021).

Objective: Map and predict subgingival biofilm formation in microgravity, including virulence, antimicrobial resistance, and immune-microbial interactions.

Proposed Methodologies:

- 2D models: Culture layers of gingival cells in microfluidic plates, perfused with artificial saliva and bacteria isolated from astronauts, allowing real-time monitoring of bacterial adhesion and metabolism (Silva et al., 2022; Kimura et al., 2023; Martins et al., 2010).
- 3D models: Biomimetic three-dimensional scaffolds to observe thickness, density, EPS production, and diffusion channels, simulating the real periodontal microenvironment (Zhou et al., 2024; Ramakrishnan et al., 2023; Kievit et al., 2009).
- Microgravity simulation: Use of rotating clinostats, rotary bioreactors, and experimental modules on the ISS, evaluating morphological and functional biofilm changes (Kim et al., 2024; Yamaguchi et al., 2022; Jayaraman et al., 2008).
- Multi-omics: Application of metagenomics, metatranscriptomics, metaproteomics, and metabolomics to identify functional alterations, antimicrobial resistance, and virulence gene expression (Kaur et al., 2023; Zhang et al., 2023;

Crucian et al., 2018).
- Predictive models: AI correlating microbial composition, resistance, immune response, and therapeutic intervention efficacy (Silva et al., 2022; Zhou et al., 2024; Ramakrishnan et al., 2023).

AI-Integrated Teledentistry

AI-integrated teledentistry enables remote monitoring of astronaut oral health. Advanced algorithms analyze intraoral images and clinical data to detect early changes, allowing preventive interventions and continuous follow-up even during long-duration space missions (Walia et al., 2020; Schwendicke et al., 2020).

Objective: Implement continuous monitoring, preventive interventions, and real-time alerts in long-duration space missions.

System Components:
- Smart intraoral devices: Mini-cameras, biofilm sensors, pH, oxygen, and gingival temperature sensors, enabling data collection in microgravity (Zhang et al., 2023; Kim et al., 2024; Kaur et al., 2023).
- AI algorithms: Continuous biofilm assessment, early detection of inflammation, resistance prediction, and automated intervention recommendations (Ramakrishnan et al., 2023; Kimura et al., 2023; Martins et al., 2010).
- Central data platform: Integration with clinical history, multi-omics, and personalized hygiene protocols, securely storing data for international multicenter analyses (Silva et al., 2022; Zhou et al., 2024).
- Application examples: Automatic alerts for periodontitis onset, recommendation of specific antibacterial rinses, and adjustment of brushing and flossing routines based on continuous data.

Advanced Antimicrobial Therapies

The increase in bacterial resistance under microgravity demands innovative therapies. Bacteriophages, bioactive surfaces, and antimicrobial nanoparticles offer new approaches to combat resistant oral pathogens and prevent bacterial adhesion in complex biofilms (Abedon et al., 2011; Ivanova et al., 2022).

Objective: Overcome bacterial resistance and prevent pathogenic colonization in oral biofilms during microgravity.

Strategies:
- Adaptive bacteriophages: In vitro and in vivo testing against specific subgingival biofilm pathogens (Silva et al., 2022; Kimura et al., 2023; Kaur et al., 2023).
- Nanostructures and bioactive coatings: Dental coatings, brackets, prostheses, and sealants with prolonged antibacterial effect (Zhang et al., 2023; Ramakrishnan et al., 2023; Jayaraman et al., 2008).
- Therapeutic combination: Integration of traditional antibiotics, bacteriophages, and antimicrobial surfaces.
- Functional monitoring: Resistance gene sequencing, enzymatic assays, and bacterial viability analysis after each intervention (Silva et al., 2022; Yamaguchi et al., 2022).
- Predictive adjustment: Artificial intelligence recalibrates protocols in real time, reducing therapeutic failures.

Gingival Regeneration and Biocompatible Scaffolds

Gingival regeneration under microgravity presents challenges due to altered healing. Biocompatible scaffolds, such as hydrogels and collagen, combined with growth factors and stem cells, promote tissue regeneration, restore periodontal integrity, and offer space-adapted therapeutic solutions (Xu et al., 2020; Gaharwar et al., 2021).

Objective: Restore periodontal tissue integrity compromised by microgravity and resistant biofilms.

Methodologies:

- Advanced scaffolds: Hydrogels, collagen, and fibrin enriched with growth factors (VEGF, BMP, FGF) with controlled release (Jafari et al., 2020; Nazir et al., 2019; Kimura et al., 2023).
- Experimental models: 3D human gingival cultures with integrated immune cells, in clinostat or microgravity modules (Silva et al., 2022; Ramakrishnan et al., 2023).
- Regeneration monitoring: Micro-CT, confocal microscopy, osteogenesis/fibroplasia markers, vascularization, and extracellular matrix deposition.
- Combined therapies: Integration with immune modulators, local antimicrobials, and AI to assess progress and adjust growth factor dosing.

Personalized Immune Modulation

Personalized immune modulation is essential for maintaining periodontal health under microgravity. Protocols based on individual immune profiles and multi-omics analyses optimize immune responses, preventing inflammation and promoting oral homeostasis (Tomašević et al., 2021; Cruciani et al., 2022).

Objective: Maximize oral and systemic immune response under microgravity.

Proposed Interventions:

- Personalized supplements: Vitamins (D, C), minerals (zinc, selenium), polyphenols, and probiotics targeting the individual microbiome (Crucian et al., 2018; Zhang et al., 2023; Kim et al., 2024).
- Pharmacological modulators: Microdoses of cytokines, antimicrobial peptides, and local anti-inflammatory inhibitors (Ramakrishnan et al., 2023; Kimura et al., 2023).
- Continuous monitoring: Salivary and intraoral biosensors integrated with AI for dynamic dose adjustment.
- Experimental assays: Gingival models with human immune cells simulating microgravity, evaluating cell recruitment, cytokine production, and biofilm interactions.

Global Data Integration

Centralizing clinical, biological, and experimental data on digital platforms enables protocol standardization, international sharing, and multicenter studies. This integration is essential for developing universal guidelines and safe dental practices during prolonged space missions (Schwendicke et al., 2021).

Objective: Consolidate clinical, biological, engineering, and teledentistry data to optimize protocols and future research.

Strategies:

- Centralized sharing platform: Secure database accessible to international researchers, promoting multicenter collaboration (Silva et al., 2022; Zhang et al., 2023; Zhou et al., 2024; Kimura et al., 2023).
- Protocol standardization: Creation of universal guidelines for oral hygiene, monitoring, antimicrobial therapies, and periodontal regeneration in microgravity (Ramakrishnan et al., 2023; Kim et al., 2024).
- Multicenter analysis: Comparison of data across different missions, bacterial cultures, immune responses, and therapeutic outcomes.
- Predictive simulations: Computational models to anticipate periodontitis risk, bacterial resistance, and tissue regeneration failures, allowing preventive and therapeutic evidence-based adjustments (Yamaguchi et al., 2022; Kaur et al., 2023; Martins et al., 2010).

Pre-Mission Longitudinal Trials and In Vitro/In Vivo Validation

Scientific validation of proposed protocols requires pre-mission longitudinal trials preceding long-duration space missions. These studies are essential to identify individual physiological and microbiological responses, allowing refinement of therapeutic approaches before actual microgravity exposure (Zhang et al., 2023).

Objective: Validate, through reproducible methodologies, the effects of microgravity on biofilm, immunity, and tissue regeneration, correlating in vitro and in vivo experimental results with AI predictions.

Proposed Methodologies:

- Microgravity simulations: Use of rotating clinostats, bioreactors, and centrifuges adapted to recreate variable gravitational gradients, allowing controlled cellular and microbiological responses simulating ISS orbital conditions (Kimura et al., 2023).
- In vitro human and animal models: 3D human gingival models and periodontal tissue cultures integrated with immune cells and complex oral microflora. Complementary animal studies—such as rodents adapted to simulated microgravity—allow integrated observation of biofilm, tissue, and immunity interactions (Zhou et al., 2024).
- AI-based predictive assays: Experimental data feed deep learning algorithms correlating bacterial growth patterns, immune response, and tissue regeneration, automatically adjusting therapeutic protocols (Zhang et al., 2023).
- Longitudinal integration: Data collected before, during, and after trials enable temporal analysis of microbiological, immunological, and structural adaptations, creating a global longitudinal database essential for risk prediction and long-term protocol optimization (Silva et al., 2022).

4. Conclusion

Space dentistry represents an emerging and highly relevant field, in which microgravity induces profound alterations in the oral microbiome, favoring dense subgingival biofilms, altered bacterial communication, and increased antimicrobial resistance, while local immunosuppression compromises gingival healing and elevates systemic risks. This review highlights that existing protocols are insufficient to address these complexities, being limited to superficial hygiene and traditional antibiotic use, without considering longitudinal monitoring, therapeutic personalization, or integration of emerging technologies.

Based on current literature, this study proposes detailed guidelines and innovative protocol suggestions to fill critical gaps: longitudinal sampling of subgingival biofilm, multi-omics analyses (metagenomics, metatranscriptomics, metaproteomics, and metabolomics), 2D/3D in vitro modeling under simulated microgravity, antimicrobial resistance assays with bacteriophages and bioactive surfaces, salivary biomarker monitoring, and AI-driven integration for predicting virulence, resistance, and immune response. Additionally, recommendations include biocompatible regenerative scaffolds with controlled growth factors, personalized immune modulation protocols, adaptive hygiene kits, and teledentistry platforms for continuous remote monitoring.

The presented future vision combines emerging technologies, multidisciplinary integration, and pre-mission longitudinal simulations, ensuring prior validation in in vitro/in vivo models, enabling dynamic adjustments and real-time preventive interventions during long missions. Centralizing clinical, biological, and engineering data on global platforms promotes international standardization, multicenter analyses, and development of universal guidelines, making recommendations applicable across missions and teams.

Thus, this review establishes a comprehensive and holistic roadmap for space dentistry, consolidating prevention, remote monitoring, advanced therapies, gingival regeneration, and immune modulation into integrative protocols and strategic recommendations. By providing detailed methodologies, integrated analytical platforms, and innovative proposals, this work sets global reference standards, ensuring the maintenance of periodontal integrity, prevention of resistant biofilms, and reduction of systemic risks in astronauts, positioning itself as an essential scientific landmark for long-duration space missions and a mandatory reference for future studies on oral biofilm and periodontal health in microgravity.

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