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Review

Oral Microbiome Research in Biopsy Samples of Oral Potentially Malignant Disorders and Oral Squamous Cell Carcinoma and Its Challenges

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Abstract: This study aims to evaluate the potential benefits and challenges of integrating oral microbiome research into the clinical management of oral potentially malignant disorders (OPMD) and oral squamous cell carcinoma (OSCC). The oral microbiome has gained significant attention for its role in the pathogenesis and progression of these conditions, with emerging evidence suggesting its value as a diagnostic and prognostic tool. By critically analyzing current evidence and methodological considerations, this manuscript examines whether microbiome analysis in biopsy samples can aid in the early detection, prognosis, and management of OPMD and OSCC. The complexity and dynamic nature of the oral microbiome require a multifaceted approach to fully understand its clinical utility. Based on this review, we conclude that studying the oral microbiome in this context holds significant promise but also faces notable challenges, including methodological variability and the need for standardization. Ultimately, this manuscript addresses the question, "Should such research be undertaken, given the intricate interactions of various factors and the inherent obstacles involved?", and also emphasizes the importance of further research to optimize clinical applications and improve patient outcomes.

Keywords: oral microbiome; oral potentially malignant disorders; oral squamous cell carcinoma; influencing factors; obstacles

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1. Introduction

Oral potentially malignant disorders (OPMD) encompass a variety of clinical entities that carry a risk of progression to oral squamous cell carcinoma (OSCC), a subtype of head and neck squamous cell carcinoma (HNSCC) [1–3]. These disorders, including leukoplakia, erythroplakia, oral lichen planus, proliferative verrucous leukoplakia, actinic cheilitis and oral submucous fibrosis, present unique challenges in clinical management and prognosis due to their unpredictable nature. OSCC represents a significant portion of head and neck cancers, characterized by high morbidity and mortality rates [1,4,5]. The transformation from OPMD to OSCC is influenced by multiple factors, including genetic mutations, environmental exposures, and the microbial environment of the oral cavity. The oral microbiome, comprising diverse microbial communities, plays a critical role in maintaining oral health and might play a pivotal role in the pathogenesis of OSCC through mechanisms like enhancing inflammation, modulating the immune system, and direct

microbial carcinogenesis, which all lead to promoting carcinogenic pathways and influencing the tumor microenvironment [6–11]. For instance, chronic inflammation induced by pathogenic bacteria like *Porphyromonas gingivalis* and *Fusobacterium nucleatum* has been shown to promote inflammatory responses that can lead to DNA damage, creating a pro-carcinogenic environment and subsequently predisposing to cancer development [8,12–15]. Immune modulation by the oral microbiome is another critical aspect, as it influences the tumor microenvironment by interacting with immune cells and other components within the oral cavity. This interaction can modulate the immune response, potentially allowing tumor cells to evade immune surveillance. The interaction between microbial communities and the host's immune system can either promote or inhibit carcinogenesis. Dysbiosis, or an imbalance in the microbial community, may lead to immune dysregulation, facilitating the persistence and progression of OPMDs [6,14,16–18]. In addition to bacterial communities, the oral microbiome includes other microbial groups, such as fungi, viruses, and protozoa, that are increasingly recognized for their potential roles in OPMD and OSCC pathogenesis. Research showed that fungi like *Candida albicans* and viruses such as Epstein–Barr virus and human papillomavirus (HPV) may interact with bacterial communities to exacerbate dysbiosis, influence inflammatory responses, and impact disease progression [19]. Despite their relevance, most studies have concentrated on bacterial microbiomes, highlighting the need for broader research into these other microbial groups in OPMD and OSCC biopsy samples. Analysis of the microbial profiles in OSCC patients has revealed significant differences compared to healthy controls, indicating that specific microbial signatures could potentially serve as biomarkers for early detection and prognosis of OSCC [20]. Direct microbial carcinogenesis involves the production of carcinogenic compounds by specific bacterial species, promoting carcinogenic pathways by metabolizing dietary components. For instance, *Fusobacterium nucleatum* has been implicated in the promotion of tumorigenesis through its ability to invade epithelial cells and modulate cellular pathways involved in cell proliferation and apoptosis by modulating the E-cadherin/β-catenin signaling pathway, a mechanism that might also be relevant in OSCC [20,21]. Studies have shown that dysbiosis may contribute to the pathogenesis of OPMD, making it crucial to understand these microbial alterations for early detection and prevention [22,23]. Research indicates that microbial signatures differ significantly between healthy tissue and OPMD lesions. For example, the presence of *Treponema denticola* and *Tannerella forsythia* has been linked to an increased risk of malignant transformation in patients with leukoplakia and erythroplakia [24]. Moreover, study conducted by Gopinath et al. [25] comparing biopsy samples, saliva, and swabs has identified key differences in microbial profiles. Biopsy samples, which represent localized lesions, often showed specific microbial communities such as *Fusobacterium nucleatum* and *Treponema denticola*, whereas saliva and swab samples provided a broader, less specific overview of oral microbial diversity. These differences underline the complementary value of these sampling methods in understanding the microbiome's role in OPMD and OSCC. Recent studies have demonstrated that alterations in the oral microbiome can contribute to the pathogenesis and progression of these conditions, highlighting the potential for microbiome analysis as a diagnostic and prognostic tool [6,18]. Emerging evidence also suggests that the oral microbiome can influence the efficacy of cancer therapies. For example, the presence of certain bacterial species has been linked to resistance to chemotherapy and radiotherapy in OSCC patients, highlighting the potential of microbiome modulation as an adjunctive treatment to improve therapeutic outcomes [26]. Specific bacterial species such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis* have been associated with OSCC, suggesting that targeted microbiome profiling could enhance early detection and personalized treatment strategies [9,22,23]. This approach underscores the potential of microbiome profiling as a non-invasive diagnostic and prognostic tool in clinical practice. However, factors such as sampling methods, microbial diversity, host–microbe interactions, and the influence of environmental and lifestyle factors are critical to understanding the complex relationship between the oral microbiome and oral carcinogenesis [27,28]. The heterogeneity in sample collection techniques—ranging from saliva, over swabs, to tissue biopsies—can

significantly impact the microbial composition and subsequent analyses. While saliva and swabs provide less invasive alternatives, biopsy samples offer critical insights into the localized tumor microenvironment, capturing unique microbial–host interactions and lesion-specific microbial communities associated with OPMD and OSCC [19]. Furthermore, the dynamic nature of oral microbiome, influenced by diet, oral hygiene practices, and systemic health, necessitates comprehensive and longitudinal studies to delineate causative relationships. Moreover, technological advancements and methodological challenges in microbiome research emphasize the need for standardized protocols and robust bioinformatic analyses [29,30]. High-throughput sequencing technologies and advanced computational tools have revolutionized our ability to profile microbial communities with unprecedented depth and accuracy. However, interpreting these complex datasets requires meticulous bioinformatics workflows to account for potential biases and confounding factors. While salivary sampling offers a non-invasive alternative for microbiome analysis, this review focuses on biopsy sampling for several reasons. First, biopsy samples allow for direct microbiome profiling at the site of pathological changes, providing more precise insights into localized microbial interactions within OPMD and OSCC lesions. Saliva represents a pooled sample of the entire oral cavity and may dilute or obscure microbial signatures specific to lesions, limiting its diagnostic specificity [31,32]. Second, biopsy samples can capture intricate host–microbe interactions within the tumor microenvironment, which are critical for understanding mechanisms of carcinogenesis [33,34]. Finally, while biopsies are more invasive, they are typically performed as part of standard diagnostic procedures in suspected OPMD or OSCC cases [35,36]. Therefore, utilizing these samples for microbiome analysis leverages existing clinical workflows without necessitating additional procedures. This review aims to evaluate the significance of oral microbiome research specifically in biopsy samples of OPMD and OSCC. By critically assessing current literature and methodological considerations, we address the key question: "Is it beneficial to conduct such research, given the complex interplay of various factors and inherent obstacles?" Although biopsy sampling has limitations, such as its invasive nature and challenges in repeatability during long-term follow-ups, its potential for providing precise, localized insights justifies its focus in this context. Our goal is to provide a comprehensive overview of the potential and challenges of integrating oral microbiome analysis into clinical practice for the early detection, prognosis, and management of OPMD and OSCC, ultimately informing future research and improving patient outcomes.

2. The Influence of Different Factors on Oral Microbiome

2.1. Age, Sex, Race/Ethnicity and Genetic Makeup

Age, sex, and race/ethnicity are demographic factors that significantly influence the composition and diversity of the oral microbiome. Aging is associated with changes in microbial diversity, often leading to a decrease in beneficial microbial populations and an increase in pathogenic species [37]. This shift may be due to age-related changes in immune function, oral hygiene practices, and salivary composition. For instance, studies have shown that the elderly tend to have higher levels of periodontal pathogens compared to younger individuals, which may contribute to chronic inflammation and a higher susceptibility to OPMD and OSCC [38–41]. Sex differences can also impact the oral microbiome, potentially through hormonal regulation. Hormones such as estrogen and testosterone can influence the microbial environment, leading to variations in microbiome composition between males and females [42]. For example, hormonal fluctuations during puberty, menstruation, pregnancy, and menopause can affect the balance of microbial communities in the oral cavity, potentially influencing the development of OPMD and OSCC [43,44]. Ethnic variations in diet and genetics further contribute to differences in the oral microbiome. Dietary habits, which vary widely across different ethnic groups, play a crucial role in shaping the microbiome. For instance, diets rich in carbohydrates and sugars can promote the growth of cariogenic bacteria, whereas diets high in fruits and vegetables support a more diverse and balanced microbial community [45]. Moreover, these differences may

affect susceptibility to OPMD and OSCC. For example, certain dietary habits prevalent in specific ethnic groups can influence the prevalence of oral pathogens associated with carcinogenesis [41]. Genetic factors also influence the oral microbiome by affecting host immune responses and susceptibility to microbial colonization. Studies have demonstrated significant differences in the oral microbiomes of different racial and ethnic groups, which may be linked to both genetic predispositions and cultural practices [46,47]. Genetic factors play a critical role in determining the composition of the oral microbiome, influencing individual susceptibility to microbiome alterations and disease development [46,48]. The interplay between host genetics and microbial communities can shape the oral environment, affecting how the microbiome responds to various external and internal factors. The human genome encodes for proteins that influence the immune system, mucosal surfaces, and salivary composition, all of which can impact the oral microbiome. Genetic variations, such as single nucleotide polymorphisms (SNPs), can affect immune responses and the ability to control microbial populations. For example, genetic polymorphisms in the *IL-1* gene cluster have been associated with increased inflammatory responses and a higher risk of periodontitis [49]. Host genetics also play a role in the production and composition of saliva, which is essential for maintaining oral health. Saliva contains antimicrobial proteins, enzymes, and immunoglobulins that help regulate the microbial communities in the oral cavity. Genetic differences in salivary protein expression can influence the oral microbiome composition, potentially affecting the prevalence and severity of oral diseases [50]. Furthermore, studies have shown that genetic makeup can determine the baseline composition of the oral microbiome, with specific bacterial taxa being more prevalent in certain genetic backgrounds. For instance, twin studies have revealed that the oral microbiomes of monozygotic twins are more similar to each other than to those of dizygotic twins, indicating a strong genetic component in microbiome composition [51]. These findings suggest that individuals with certain genetic backgrounds may be predisposed to specific microbial profiles, which could influence their risk of developing oral diseases. Research has also highlighted the role of genetic makeup in the susceptibility to microbiome-related diseases. For example, variations in the *DEFB1* gene, which encodes for β-defensin 1, an antimicrobial peptide, have been linked to differences in susceptibility to dental caries. Individuals with certain *DEFB1* polymorphisms may have reduced antimicrobial activity in their saliva, leading to a higher risk of cariogenic bacterial colonization and caries development [52]. In addition, oral microbiome can interact with the host's genetic factors to modulate disease progression and outcomes. For instance, genetic predispositions to inflammatory responses can exacerbate the effects of microbial dysbiosis, leading to more severe periodontal disease or higher susceptibility to oral infections. Genetic variations can also influence immune responses and the ability to control microbial populations, thereby affecting the risk of OPMD and OSCC. For instance, polymorphisms in immune-related genes have been associated with increased inflammatory responses and a higher risk of OSCC [53]. Understanding the genetic influences on the oral microbiome can help identify individuals at risk and develop personalized strategies for prevention and treatment [54].

2.2. Diseases

2.2.1. Chronic Systemic Diseases

Family history and chronic diseases such as endocarditis, diabetes, Crohn's disease, ulcerative colitis, and gastrointestinal malignancies significantly impact the oral microbiome [55]. These conditions alter systemic inflammation and immune responses, thereby influencing oral microbial communities [56–68]. For instance, diabetes is well known for its effects on the oral microbiome, leading to increased levels of pathogenic bacteria and a higher prevalence of periodontal disease. The hyperglycemic environment in diabetic patients promotes microbial growth and inflammation, resulting in a dysbiotic oral microbiome, characterized by increased levels of pathogenic bacteria such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* [56]. These bacteria are known to promote chronic inflammation and have been implicated in the pathogenesis of OSCC. The

persistent inflammatory state and impaired immune response in diabetes may facilitate the malignant transformation of OPMD to OSCC [69]. Similarly, chronic inflammatory diseases like Crohn's disease and ulcerative colitis can affect oral microbial populations due to the systemic inflammatory burden they impose. Patients with these conditions often exhibit altered oral microbiomes, with increased presence of pro-inflammatory bacteria, which may contribute to the development of OPMD and its progression to OSCC [57–62,70]. Gastrointestinal malignancies, such as colorectal cancer, can also influence the oral microbiome. Studies have shown that patients with gastrointestinal cancers often have distinct oral microbial profiles, which may reflect the systemic changes in the immune system and the inflammatory milieu associated with OSCC [63]. These alterations in the oral microbiome could potentially serve as non-invasive biomarkers for early detection and monitoring of these malignancies [64,65]. Endocarditis, an infection of the inner lining of the heart, is another condition that significantly impacts the oral microbiome. The presence of specific oral pathogens, such as *Streptococcus mitis* and *Fusobacterium nucleatum*, has been linked to an increased risk of this chronic disease. These bacteria can enter the bloodstream through periodontal lesions, leading to systemic infections. The chronic inflammatory state induced by these pathogens may create a pro-carcinogenic environment in the oral cavity, possibly facilitating the development and progression of OPMD to OSCC [66–68,71].

2.2.2. Current Viral Infections

Acute viral infections, such as the common cold or flu, can transiently disrupt the oral microbiome, leading to shifts in microbial composition that may impact oral health [72,73]. These infections cause inflammation and immune responses that can alter the balance of microbial communities in the oral cavity. During a viral infection, the immune system's response to the virus often includes the production of cytokines and other inflammatory mediators, which can affect the oral environment. This inflammatory response can lead to changes in the microbial composition, such as an increase in opportunistic pathogens and a decrease in beneficial commensal bacteria. For example, the flu virus has been shown to increase the levels of pathogenic bacteria like *Streptococcus pneumoniae* and *Haemophilus influenzae* in the oral cavity, potentially leading to secondary bacterial infections, which may exacerbate inflammation and tissue damage in the oral cavity [74–76]. Furthermore, the common cold can result in alterations to the oral microbiome due to changes in salivary flow and composition, which are crucial for maintaining microbial homeostasis. Reduced salivary flow and the presence of inflammatory exudates can create a favorable environment for the growth of pathogenic microorganisms [77]. Although the effects of acute viral infections are typically short-lived, repeated or prolonged infections may predispose the oral mucosa to persistent inflammation, a recognized risk factor for OPMD and OSCC. Additionally, antiviral medications and symptomatic treatments for these infections can also influence the oral microbiome by altering the chemical environment in the mouth [78]. Changes in salivary pH and composition due to medication use may exacerbate microbial imbalances, indirectly contributing to conditions that favor the progression of OPMD to OSCC [79]. Chronic viral infections, such as those caused by herpes simplex virus (HSV) or HPV, can have more prolonged effects on the oral microbiome. These infections can lead to persistent inflammation and immune modulation, further disrupting the balance of microbial communities and promoting the growth of oncogenic microbial species, contributing to development of HNSCC [44,51,80].

2.2.3. Periodontal and Peri-Implant Diseases

Acute and chronic oral infections, including severe gingivitis and periodontitis, are closely linked to changes in the oral microbiome [81,82]. These conditions can promote the growth of pathogenic bacteria and create a pro-inflammatory environment conducive to disease progression [83]. Gingivitis, an inflammation of the gingiva, is often the result of the accumulation of dental plaque, which harbors pathogenic microorganisms. The shift from a balanced microbial community to one dominated by pathogenic bacteria

such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* is a hallmark of gingivitis [84]. This dysbiotic state can trigger an inflammatory response, leading to the clinical signs of gingivitis, including redness, swelling, and bleeding of the gums [85]. Periodontitis, a more severe form of gum disease, extends beyond gingivitis, affecting the supporting structures of the teeth. The progression from gingivitis to periodontitis involves deeper microbial invasion and a more pronounced inflammatory response. Periodontitis is characterized by the destruction of the periodontal ligament and alveolar bone, which can ultimately lead to tooth loss if untreated. The oral microbiome in periodontitis patients shows a significant increase in pathogenic bacteria such as *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum*, which contribute to the disease's pathogenicity [83,86,87]. The inflammatory environment created by these infections not only exacerbates the local destruction of periodontal tissues but can also have systemic implications. Chronic periodontitis has been linked to numerous systemic conditions such as cardiovascular and neurodegenerative diseases, diabetes, inflammatory bowel disease, autoimmune diseases (e.g., rheumatoid arthritis), chronic renal insufficiency, neoplasms, as well as to fertility and adverse pregnancy outcomes, highlighting the importance of maintaining oral health for overall well-being [88]. The pro-inflammatory cytokines and mediators released during periodontitis can enter the systemic circulation, influencing distant organs and contributing to systemic inflammation [89]. Research indicates a significant association between periodontal disease and an increased risk of developing OPMD and OSCC. A case–control study found that individuals with periodontitis were more likely to have poorly differentiated OSCC compared to those without periodontitis, suggesting a potential link between periodontal disease and OSCC progression [90]. Additionally, a retrospective cohort study by Qian et al. [91] demonstrated that periodontitis and tooth loss are significantly associated with increased OSCC mortality in individuals aged $\geq$75 years. Treatment of periodontal diseases involves mechanical removal of dental plaque and tartar, alongside antimicrobial therapies to reduce the bacterial load. Recent advancements in microbiome research suggest that probiotic and prebiotic treatments may also help restore a healthy microbial balance in the oral cavity, providing a novel approach to managing these conditions [92]. Similarly, peri-implant diseases—conditions affecting the tissues surrounding dental implants—are influenced by dysbiosis in the microbiome. Peri-implant health is associated with a balanced microbial community dominated by commensal species, whereas peri-implant mucositis, an early inflammatory condition, shows increased levels of pathogenic bacteria. Key pathogens such as *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Porphyromonas gingivalis* have been implicated in mucositis, which, if left untreated, may progress to peri-implantitis [93–95]. Peri-implantitis involves extensive tissue destruction, including alveolar bone loss, and exhibits a microbial profile more dominated by anaerobic Gram-negative bacteria, such as *Treponema denticola* and *Aggregatibacter actinomycetemcomitans*, akin to periodontitis [96]. The changing microbiota in peri-implant conditions reflects the dynamic host–microbe interaction. This altered microenvironment may facilitate malignant transformation in the surrounding tissues. A clinical retrospective analysis reported cases where peri-implant oral malignancies, primarily OSCC, developed in patients previously treated for peri-implantitis, highlighting the potential for malignant transformation associated with peri-implant diseases [97]. Treatment strategies of peri-implant diseases often involve mechanical debridement and antimicrobial agents, with adjunctive therapies, such as probiotics, showing promise in restoring microbial balance [98]. Recent advancements in microbiome research further suggest that understanding the specific shifts in microbial communities across periodontal and peri-implant diseases may guide personalized therapeutic approaches.

2.3. Lifestyle Factors

Lifestyle factors such as smoking, alcohol consumption, drug use, and specific diets profoundly affect the oral microbiome. These behaviors can lead to significant shifts in the composition and diversity of microbial communities in the oral cavity, often with detrimen-

tal effects on oral health. Smoking is one of the most well-documented lifestyle factors that negatively impacts the oral microbiome. Smokers typically exhibit a decrease in beneficial microbial populations and an increase in pathogenic species, such as *Porphyromonas gingivalis* and *Tannerella forsythia*, which are associated with periodontal disease and have been implicated in oral carcinogenesis [99]. The carcinogenic compounds in tobacco smoke can cause direct DNA damage and promote a pro-inflammatory environment, facilitating malignant transformation of OPMD to OSCC [100–103]. Alcohol consumption also significantly alters the oral microbiome and is linked to an elevated risk of OSCC. Regular alcohol intake can reduce microbial diversity and increase the abundance of harmful bacteria, such as *Streptococcus mutans*, which is linked to dental caries [104]. Alcohol can disrupt the balance of the oral microbiome by altering the pH and providing a nutrient-rich environment for acidogenic and aciduric bacteria. Additionally, alcohol can impair salivary flow, further exacerbating microbial imbalances and increasing the risk of oral diseases [105,106]. Additionally, alcohol metabolism produces acetaldehyde, a known carcinogen, which can accumulate in the oral cavity, especially in individuals with poor oral hygiene or those who smoke, further increasing cancer risk [103]. Drug use, particularly the use of recreational drugs like methamphetamines and opioids, can have severe consequences for the oral microbiome. These substances often lead to poor oral hygiene, dry mouth (xerostomia), and changes in the oral environment that favor the growth of pathogenic bacteria. Zhang et al. [107] have demonstrated that drug users have alterations in the oral microbiome and are more likely to suffer from periodontal disease and dental caries. The resulting chronic inflammation and tissue damage may increase the susceptibility to OPMD and OSCC [103]. Dietary choices play a crucial role in modulating the diversity and composition of the oral microbiome. Diets high in sugars and refined carbohydrates promote the growth of cariogenic bacteria such as *Streptococcus mutans* and *Lactobacillus* spp., which can lead to dental caries [108]. Conversely, diets rich in fruits, vegetables, and fiber support a more diverse and balanced microbial community. These diets can increase the presence of beneficial bacteria, such as *Streptococcus sanguinis* and *Lactobacillus gasseri*, which are associated with good oral health [109]. The Mediterranean diet, which is high in fruits, vegetables, nuts, and whole grains, has been shown to positively influence the oral microbiome by enhancing microbial diversity and promoting the growth of beneficial species [110,111]. Similarly, probiotic-rich foods like yogurt and fermented vegetables can help maintain a healthy balance of oral bacteria, potentially reducing the risk of oral diseases such as OPMD and OSCC.

2.4. Local Factors, Socioeconomic Status and Sexual Habits

Social status and sexual habits, as well as the presence of local factors such as wearing dentures, significantly influence the oral microbiome. These factors can alter the balance of microbial communities in the oral cavity, impacting overall oral health. Poor oral hygiene, often associated with lower social status, is a major contributor to oral dysbiosis. Individuals from lower socioeconomic backgrounds may have limited access to dental care and education on proper oral hygiene practices, leading to the accumulation of dental plaque and the growth of pathogenic bacteria. This can result in an increased prevalence of oral diseases such as gingivitis, periodontitis, and dental caries [112]. Studies have shown that socioeconomic factors are strongly correlated with oral health outcomes, with lower social status being linked to higher levels of harmful bacteria like *Streptococcus mutans* and *Porphyromonas gingivalis* which may predispose the oral mucosa to persistent inflammation and therefore contribute to oral carcinogenesis [113–115]. The presence of dentures can also impact the oral microbiome. Dentures create new surfaces for microbial colonization and can harbor pathogenic bacteria if not properly maintained. Poor denture hygiene can lead to the development of denture stomatitis, a condition characterized by inflammation of the oral mucosa caused by an overgrowth of *Candida* species and other pathogens such as *Fusobacterium nucleatum* and *Prevotella intermedia*. These changes in the microbiome contribute to an inflammatory environment that affects both the mycobiome and bacteri-

ome further contributing to oral dysbiosis and possibly oral carcinogenesis [116,117]. The microbial alterations in denture wearers have been shown to vary depending on the type of prosthesis (implant-supported vs. non-implant-supported) and the health status of the oral mucosa. Research indicates that the oral bacteriome in denture wearers exhibits increased diversity, with an overrepresentation of pathogens compared to individuals without prostheses. This shift underscores the importance of regular denture cleaning, appropriate fitting, and routine dental check-ups to prevent dysbiosis and associated infections [118]. Sexual habits play a significant role in introducing new microbial strains into the oral cavity. Oral–genital contact can transfer microorganisms between partners, potentially altering the oral microbiome. For instance, HPV and other sexually transmitted infections (STIs) can be transmitted through oral sex, introducing new viral and bacterial species that may affect oral health. The oral microbiome composition can change with the introduction of these new microorganisms, potentially leading to dysbiosis and increasing the risk of oral and systemic infections as well as possibly promoting oral carcinogenesis [119–121].

2.5. Hormonal Influences in Pregnancy and Menopause

Pregnancy induces significant hormonal changes that affect the oral microbiome [122]. Elevated levels of hormones such as estrogen and progesterone during pregnancy can alter the microbial environment in the oral cavity, often leading to an increase in periodontal pathogens. This hormonal influence can exacerbate conditions like gingivitis and periodontitis, commonly referred to as pregnancy gingivitis [123]. Ye et al. [124] have shown that pregnant women are more susceptible to oral infections due to these hormonal fluctuations, leading to an increase in periodontal pathogens such as *Porphyromonas gingivalis* and *Prevotella intermedia*. These bacteria exacerbate periodontal inflammation, creating a chronic inflammatory state in the oral cavity. Chronic inflammation is a recognized risk factor for OPMD and may facilitate the malignant transformation of premalignant lesions into OSCC. Additionally, the immune modulation associated with pregnancy may reduce the host's ability to control oncogenic microbial species, further increasing the risk of OPMD and OSCC [125]. Similar influences are observed during other periods of hormonal fluctuation, such as menopause, where declining estrogen levels contribute to changes in microbial diversity and an increased prevalence of oral diseases such as OPMD and OSCC [126]. Furthermore, estrogen deficiency has been linked to a decrease in salivary antimicrobial peptides, which can allow carcinogenic microbial species to proliferate, potentially contributing to oral carcinogenesis [127,128]. The interplay between hormonal changes, dysbiosis, and inflammation highlights the importance of tailored oral care during pregnancy and other hormonally dynamic life stages. Gender-related hormonal factors, including the use of oral contraceptives, can also affect microbial composition and the host immune response, further promoting dysbiosis and carcinogenesis, potentially increasing the likelihood of OPMD and OSCC in susceptible individuals [129].

2.6. Medication Use and Probiotic Consumption

Medications such as antibiotics, antimycotics, corticosteroids, methotrexate, and immunosuppressive agents can significantly disrupt the microbial balance in the oral cavity. The dysbiotic shifts and immune suppression caused by medications contribute to chronic inflammation and microbial imbalances, key factors in the pathogenesis of OPMD and OSCC. Understanding these effects is crucial for mitigating risks in patients requiring long-term medication use [130–134]. Antibiotics, for example, can reduce microbial diversity by eliminating both harmful and beneficial bacteria, potentially leading to overgrowth of resistant strains and opportunistic pathogens [130,131]. Corticosteroids and immunosuppressive agents, used to manage inflammatory and autoimmune conditions, can suppress the immune response, thereby affecting the oral microbiome. These medications can create an environment that favors the proliferation of opportunistic pathogens, increasing the risk of oral infections such as candidiasis [132,133]. Methotrexate, a common immunosuppressive drug, has been shown to alter the oral microbiome by reducing the abundance

of certain bacterial species and promoting the growth of others, leading to a dysbiotic state [134]. On the other hand, emerging studies suggest that certain drugs and targeted therapies may improve the oral microbiome and contribute to disease management. For example, antifungal agents like fluconazole have demonstrated efficacy in reducing *Candida albicans* colonization, mitigating inflammation, and improving oral health outcomes in patients with oral candidiasis [135]. Furthermore, prebiotic compounds, such as inulin and fructooligosaccharides, have been shown to enhance the growth of beneficial bacteria while suppressing pathogenic species, potentially aiding in the management of dysbiosis-related conditions [136]. Immunomodulatory agents, including IL-17 inhibitors, have also been explored for their ability to reduce inflammation and restore microbial balance in periodontal diseases as well as autoimmune conditions affecting the oral cavity [137,138]. These developments highlight the potential of integrating therapeutic strategies targeting the oral microbiome into clinical practice for both prevention and treatment of oral diseases such as OPMD and OSCC. Recent probiotic use also impacts the oral microbiome. Probiotics are beneficial bacteria that, when introduced into the oral cavity, can help restore microbial balance and improve oral health. Probiotic strains such as *Lactobacillus reuteri* and *Bifidobacterium* species have been studied for their ability to reduce the levels of periodontal pathogens and promote a healthier oral microbiome [139]. These beneficial microorganisms not only counteract harmful biofilms but also help modulate the host immune response, reducing inflammation and supporting tissue health. Large doses of commercial probiotics ($\geq 10^8$ CFU mL^{-1} organisms per day) taken for 2–6 months can significantly alter the oral microbiome, promoting beneficial bacteria but potentially masking disease-related microbial changes [140,141]. The use of probiotics has shown promise in managing conditions like gingivitis, periodontitis, and even halitosis by enhancing the beneficial microbial population and inhibiting the growth of harmful bacteria [142,143]. Beyond reversing dysbiosis, probiotics play a crucial role in host modulation and biofilm control, highlighting their therapeutic potential in managing inflammatory oral diseases, including periodontal and peri-implant conditions. Probiotics can inhibit pathogenic biofilm formation, enhance the host immune response, and restore microbial balance, thereby mitigating inflammation and tissue destruction associated with these diseases, therefore possibly contributing to oral carcinogenesis [144].

2.7. Degree of Dysplasia and Disease Management

The severity of dysplasia and the management strategies employed significantly influence the oral microbiome. Advanced dysplasia often correlates with more profound microbial changes, reflecting the disease's progression and the increasingly dysbiotic environment [145–148]. Different treatments, including surgical intervention, radiation, and pharmacological therapies, can further modulate microbial communities [149–156]. Advanced dysplasia, characterized by significant cellular atypia and architectural disruption, is associated with distinct shifts in the oral microbiome. Studies have shown that severe dysplasia is often accompanied by a decrease in microbial diversity and an increase in pathogenic bacteria, such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis* [145–147]. These bacteria are known to promote inflammation and may contribute to the progression from dysplasia to carcinoma by creating a pro-carcinogenic microenvironment [148]. Disease management strategies, including surgical resection, radiation therapy, and chemotherapy, also impact the oral microbiome. Surgical interventions, while removing dysplastic lesions, can disrupt the local microbiome and promote the colonization of opportunistic pathogens during the healing process. Post-surgical microbial imbalances can lead to complications such as infections and delayed healing [149,150]. Radiation therapy, commonly used in the treatment of OSCC, can have profound effects on the oral microbiome. Radiation can damage the salivary glands, reducing salivary flow and altering the oral environment. This reduction in saliva, which has antimicrobial properties, can lead to a decrease in microbial diversity and an increase in opportunistic pathogens, such as *Candida* species, contributing to conditions like oral candidiasis [151,152]. Additionally, radiation-induced

changes in the oral microbiome can exacerbate inflammation and increase the risk of secondary infections [153]. In the study by de Freitas Neiva Lessa et al. [154], oral microbiome dysbiosis was observed in HNSCC patients, with notable shifts during radiotherapy. By the end of treatment, the dysbiosis lessened; however, elevated levels of *Fusobacterium nucleatum* and *Porphyromonas gingivalis* were associated with poorer clinical outcomes. Chemotherapy, which targets rapidly dividing cells, can also affect the oral microbiome by disrupting the balance of microbial communities. Chemotherapeutic agents can reduce the abundance of beneficial bacteria and allow for the overgrowth of resistant and pathogenic species. This dysbiosis can result in oral complications such as mucositis, candidiasis, and periodontal disease, highlighting the need for careful microbial management in patients undergoing chemotherapy [155,156]. Figure 1 illustrates a concise overview of all the previously discussed factors influencing the oral microbiome.

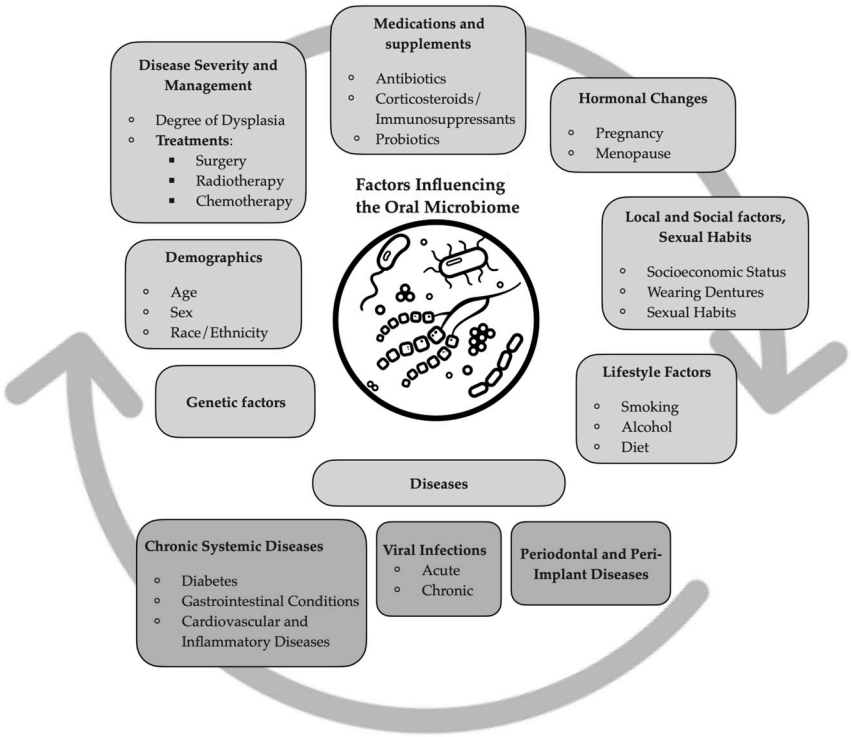

Figure 1. Key factors influencing the oral microbiome (an original scheme based on current literature data).

3. Obstacles in Oral Microbiome Studies

3.1. Sampling Issues

One of the primary challenges in oral microbiome research is the unavailability of longitudinal sampling, which limits the ability to track microbial changes over time. Longitudinal studies are essential for understanding the dynamics of the oral microbiome and its role in the progression of oral diseases. Without repeated sampling, it is difficult to determine whether observed microbial changes are transient or persistent, and how they correlate with disease development or treatment outcomes [157,158]. Additionally, limited sample sizes reduce the statistical power and generalizability of findings. Small sample sizes can lead to overestimation or underestimation of microbial associations with disease states, making it challenging to draw robust conclusions [159]. The variability in the oral microbiome across different individuals necessitates larger sample sizes to capture the diversity and complexity of microbial communities accurately [159]. Studies with insufficient sample sizes may fail to detect significant differences or correlations, leading to inconclusive or misleading results [158]. The method of sample collection also poses significant limitations. The oral cavity has various niches, including saliva, tongue, buccal mucosa, dental

plaque, and subgingival areas, each harboring distinct microbial communities. Inconsistent sampling methods can lead to variability in the data, complicating comparisons across studies. Standardized protocols for sample collection, processing, and storage are crucial to ensure consistency and reliability in oral microbiome research [159,160]. Moreover, the condition of the sample at the time of collection can affect the results. Factors such as the time of day, recent food intake, oral hygiene practices, and use of antimicrobial agents can influence the microbial composition [160]. These variables need to be controlled or accounted for in study designs and analyses of the results to minimize their impact on the findings. Another challenge is the potential contamination of samples. Oral microbiome studies are particularly susceptible to contamination from external sources, including laboratory environments and reagents used in sample processing. Rigorous controls and careful handling of samples are necessary to minimize contamination and ensure the accuracy of the results [159]. Technological limitations also play a role. While high-throughput sequencing technologies have revolutionized our ability to profile microbial communities, they come with their own set of challenges [157]. Sequencing depth, accuracy, and bioinformatic analyses can introduce biases and errors that affect the interpretation of dana [158]. The selection of sequencing platforms and analytical tools must be done with consideration of their limitations and potential impact on the study outcomes [159].

3.2. Ethical Considerations

Ethically, it is challenging to include healthy controls in microbiome studies involving OPMD and OSCC, as invasive procedures may not be justified in healthy individuals. The need to balance the scientific benefits of obtaining control samples with the ethical imperative to minimize harm to participants poses a significant dilemma in the design of such studies [161,162]. Invasive sampling methods, such as biopsies, are essential for obtaining accurate and representative microbiome data from affected tissues. However, performing these procedures on healthy individuals solely for research purposes raises ethical concerns, including the potential for harm, discomfort, and unnecessary medical risks. Ethical guidelines and institutional review boards often require that the potential benefits of research outweigh the risks to participants, making it difficult to justify invasive procedures in healthy volunteers [161,163]. To address these ethical challenges, researchers may opt for less invasive sampling methods, such as saliva or oral swabs, which can still provide valuable information about the oral microbiome without posing significant discomfort to participants. While these methods may not capture the full complexity of microbial communities associated with specific lesions, they offer a more ethically acceptable alternative for obtaining control samples [162]. Additionally, non-invasive sampling can facilitate the inclusion of a larger and more diverse cohort of healthy controls, enhancing the generalizability of study findings [163]. However, as mentioned earlier, saliva often fails to capture the lesion-specific microbial communities found in OPMD and OSCC tissues. The microbiological spectrum in biopsy samples is more localized and reflects the tumor microenvironment, including microbial–host interactions that may be missed in salivary analyses [164]. A recent umbrella review has highlighted significant differences between the microbiota profiles obtained from saliva and biopsy samples in OSCC patients. While salivary samples provide an overview of bacterial, viral, and fungal species present in the oral cavity, biopsy samples from OSCC lesions reveal specific microbial signatures more closely associated with the tumor microenvironment, such as *Fusobacterium nucleatum* and *Candida albicans*. The review emphasized the complementary nature of these methods, with salivary sampling offering a non-invasive approach for broader screening and biopsy sampling providing detailed insights critical for diagnostic and prognostic purposes [19]. Incorporating these findings into ethical considerations is essential for future research. For example, combining non-invasive salivary sampling for initial screening with selective biopsy sampling in high-risk or symptomatic cases could balance ethical imperatives with the need for comprehensive microbiome data [19]. Another ethical consideration is informed consent. Participants must be fully informed about the nature of the study,

the procedures involved, and the potential risks and benefits. Ensuring that participants understand and voluntarily agree to participate is crucial, particularly when dealing with invasive procedures. Researchers must provide clear and comprehensive information and allow participants to ask questions and withdraw from the study at any time without penalty [161]. Data privacy and confidentiality are also paramount in microbiome research. The unique nature of microbiome data, which can potentially be linked to personal health information, necessitates stringent measures to protect participant anonymity and data security. Researchers must adhere to data protection regulations and implement robust data management practices to ensure that sensitive information is not disclosed or misused [161]. Furthermore, there is an ethical obligation to ensure that the findings of microbiome research are translated into tangible benefits for the study population, particularly those suffering from OPMD and OSCC. This includes the development of improved diagnostic, prognostic, and therapeutic strategies that can enhance patient care and outcomes. Researchers should engage with patients, healthcare providers, and policymakers to ensure that research findings are effectively communicated and implemented in clinical practice [163].

3.3. Contamination Concerns

Contamination is a significant concern in oral microbiome research, as it can introduce biases and confound results. There is a risk of contamination from both the tumor surface and laboratory kits used during sample collection and processing. Contaminants can skew the microbial profiles, leading to erroneous conclusions about the microbial communities associated with OPMD and OSCC [165,166]. Contamination from the tumor surface occurs when microorganisms present on the surface of the lesion are inadvertently included in the sample. This can happen during biopsy or swab collection, especially if the sampling method is not sufficiently stringent. Surface contaminants may not accurately reflect the microbial communities within the tissue, thus leading to misleading data about the microbiome's role in disease progression [166,167]. To mitigate this, researchers must employ careful and consistent sampling techniques, ensuring that samples are taken from the deeper layers of the tissue, where the true microbial communities reside. Laboratory kit contamination is another major source of bias. DNA extraction kits, sequencing reagents, and other laboratory chemical and plastic consumables can introduce exogenous microbial DNA into the samples, contaminating the data. This is particularly problematic in microbiome studies, where the goal is to identify and characterize the microbial communities accurately. The presence of contaminant DNA can lead to false positives and obscure the true microbial signals [6,167]. To address this, researchers should use kits and reagents that are certified for low microbial contamination, and include appropriate negative controls to detect and account for any contaminants. Rigorous protocols are essential to minimize contamination risks. These protocols should include steps for ensuring sample integrity from collection through to analysis. For instance, using sterile instruments and maintaining a clean working environment can help reduce the risk of introducing contaminants during sample collection. Additionally, protocols for DNA extraction and amplification should be optimized to minimize the risk of contamination from reagents and equipment [167]. Implementing stringent quality control measures is also crucial. This includes regularly validating the sterility of consumables, performing routine checks for contamination, and using advanced bioinformatics tools to identify and exclude contaminant sequences from the data analysis [6,165]. Moreover, adopting standardized protocols across different laboratories can enhance reproducibility and comparability of results, helping to ensure that findings are robust and reliable. Collaborative efforts among researchers to share best practices and develop guidelines for contamination control can further enhance the quality of microbiome research. By addressing contamination concerns proactively, the scientific community can improve the accuracy and reliability of studies on the oral microbiome's role in OPMD and OSCC, ultimately contributing to better diagnostic and therapeutic strategies [6,166].

3.4. Causality Dilemma

A critical question in oral microbiome research is whether changes in the microbiome are a cause or a consequence of malignant transformation. This causality dilemma complicates the interpretation of findings and the development of targeted interventions. Determining the directionality of the relationship between microbial shifts and disease progression is essential for understanding the underlying mechanisms and for designing effective therapeutic strategies [168,169]. One of the primary challenges in addressing this causality dilemma is the complex interplay between the host and microbial communities. Changes in the oral microbiome may precede the development of OPMD and OSCC, suggesting a potential causative role. For instance, certain pathogenic bacteria, such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, have been implicated in promoting carcinogenesis through mechanisms like inducing inflammation, immune modulation, and direct invasion of epithelial cells [168,170]. These bacteria can create a microenvironment conducive to malignant transformation by disrupting normal cellular processes and promoting genomic instability [170]. On the other hand, malignant transformation and the associated changes in the tissue environment can also influence the composition of the oral microbiome. Tumor development can alter local conditions, such as oxygen availability, pH, and nutrient levels, which in turn can select for specific microbial populations. This suggests that observed changes in the microbiome might be a consequence rather than a cause of malignancy [169]. For example, the metabolic by-products of cancer cells, such as lactate, can provide a favorable environment for the growth of certain anaerobic bacteria, potentially leading to dysbiosis [169]. Longitudinal studies are crucial for disentangling this causality dilemma. By tracking microbial changes over time in individuals at risk of developing OPMD or OSCC, researchers can identify early microbial alterations that may serve as predictive markers of disease onset. These studies can help determine whether microbial shifts precede malignant transformation or occur as a result of it [7]. However, conducting such studies poses significant logistical and ethical challenges, particularly in obtaining repeated invasive samples from participants. Experimental models, including animal studies and in vitro systems, can also provide valuable insights into causality. These models allow for the manipulation of specific microbial populations and the observation of their effects on host tissues in a controlled environment. For example, studies using germ-free mice colonized with specific oral bacteria can help elucidate the direct effects of these microbes on tissue inflammation, immune responses, and tumor development [168]. Advanced analytical techniques, such as multi-omics approaches, can further aid in resolving the causality dilemma. Integrating genomic, transcriptomic, proteomic, and metabolomics data can provide a comprehensive view of the interactions between the host and the microbiome. This holistic approach can reveal how microbial changes influence host cellular pathways and vice versa, offering clues about the directionality of these interactions [169,170]. Understanding the causality of microbiome changes in the context of OPMD and OSCC is essential for developing targeted interventions. If specific microbial shifts are identified as causative factors, therapeutic strategies could focus on modulating the microbiome to prevent or slow down disease progression. Conversely, if microbial changes are primarily consequences of malignancy, interventions might focus on mitigating their effects to improve patient outcomes [168,169]. Figure 2 provides a concise summary of all the previously mentioned obstacles in oral microbiome studies, along with proposed solutions for each.

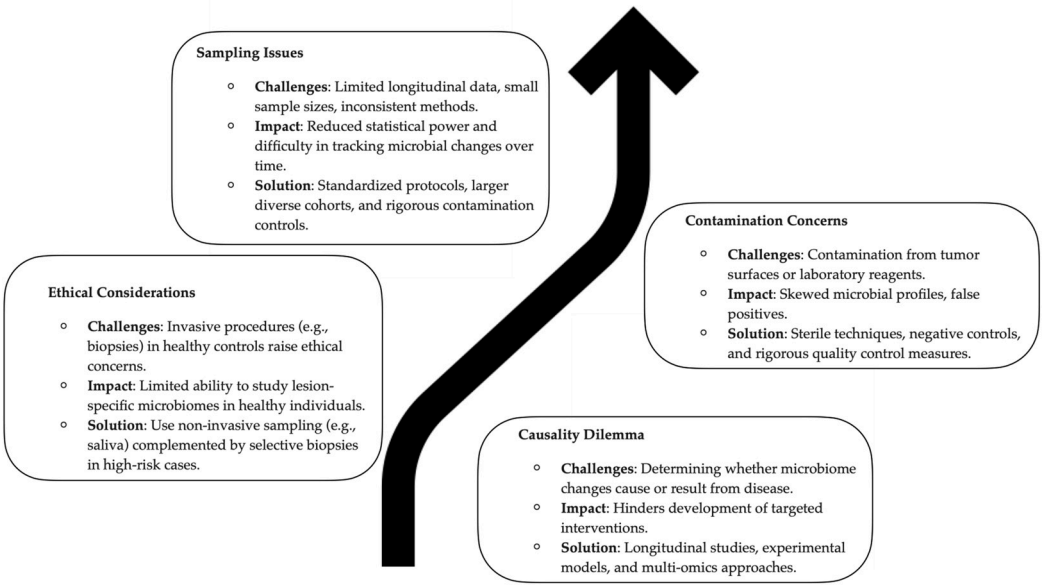

Figure 2. Key obstacles and suggested solutions in oral microbiome studies (an original scheme based on current literature data).

4. Conclusions

Understanding the oral microbiome's role in OPMD and OSCC is crucial for developing early detection strategies, preventive measures, and novel therapies. While current research highlights the potential significance of microbial alterations, various factors and obstacles must be considered. Addressing these challenges will require comprehensive, well-designed studies with larger sample sizes, longitudinal sampling, and robust methodologies to mitigate contamination risks and ethical concerns. Future research should focus on elucidating the causal relationships between the microbiome and malignant transformation to unlock the full potential of microbiome-based interventions in OSCC prevention and treatment.

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