https://doi.org/10.62587/AFRJMS.2.2.2025.77-81 ISSN: 3006-7421

African Research Journal of Medical Sciences

Journal homepage: https://www.afrjms.com

Communication **Open Access**

Reemerging importance of methanogenic archaea in the landscape of periodontal disease

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Article Info

Volume 2, Issue 2, July 2025
Received : 14 March 2025
Accepted : 07 July 2025
Published : 25 July 2025
doi: 10.62587/AFRJMS.2.2.2025.77-81

Abstract

Periodontal disease is the most common chronic inflammatory condition with a polymicrobial origin, particularly among the elderly. Numerous risk factors can independently or synergistically contribute to immune suppression and inflammation in the periodontium. This leads to microbial dysbiosis in the periodontal pockets and the supra gingival biofilm, resulting in the elevation of pathobionts or opportunistic pathogens that are considered potential contributors to periodontal disease. The progression from gingivitis to chronic periodontitis typically follows an ecological succession, starting with the facultative anaerobes of the yellow complex and advancing to the strict anaerobes of the red complex of periodontal pathogens. Additionally, there has been an observed increase in Sulfate-Reducing Bacteria (SRB) within the oral cavities, which are part of the human oral microbiome. SRB is a diverse group of naturally occurring microorganisms known for their capability of dissimilatory sulfate reduction to Hydrogen Sulfide (H_2S). Methanogenic archaea are a minority within the SRB group, known for their hydrogenotrophic metabolism and cooperative growth alongside other species in the periodontal pockets. However, these methanogenic archaea are not typically recognized as contributors to the development of periodontal disease. Investigating the role of methanogenic archaea in the context of periodontal disease enhances our understanding of the dynamics within the supragingival biofilm associated with chronic periodontitis.

Keywords: *Periodontal disease, Methanogenic archaea, Sulfate-reducing bacteria, Syntrophic interactions, Hydrogenotrophic metabolism*

The oral cavity hosts at least 700 bacterial species, along with a diverse range of fungi, archaea, viruses, and protozoa (Perera *et al.*, 2023). Archaea represent one of the three domains of life (Woese *et al.*, 1990; Sogodogo *et al.*, 2019) alongside bacteria and eukaryotes—based on their unique genetic, structural,

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and biochemical characteristics (Ashok *et al.*, 2013). Methanogenic archaea, are commonly found in anaerobic environments, such as wetlands, rice fields, and biological treatment systems, as well as in the gastrointestinal tracts of ruminants (Horz and Conrads, 2011). Additionally, these methane-producing organisms have been detected in the oral cavity (Eva *et al.*, 2001), gastrointestinal tract (Miller and Wolin, 1982), of humans and vagina (Belay *et al.*, 1990) of women. Methanogenesis, the process through which they produce methane (CH_4), requires the presence of hydrogen (H_2) to reduce carbon dioxide (CO_2) into methane as they are on hydrogenotrophic metabolism (Sogodogo *et al.*, 2019; Triantafyllou *et al.*, 2014). Culture-based methods, along with gas chromatography, have been used to detect methanogenic archaea in oral samples. In addition, molecular techniques that target the 16S rRNA gene or the functional gene mcrA—which encodes for Methyl-Coenzyme M reductase, a key enzyme involved in methanogenesis—are employed (Horz and Conrads, 2011). Molecular techniques especially 16S rRNA sequencing undermine the culture based techniques with inherent limitations (Horz and Conrads, 2011). These detection methods identify *Methanobrevibacter oralis* as the predominant methanogenic archaea in the oral cavity (Huynh *et al.*, 2015). Other species, such as *Methanobrevibacter smithii* and *Methanosphaera stadtmanae*, *Methanosarcina mazei*, *Methanobacterium curvum/ congolense* and *Thermoplasmata* have been encountered on lower prevalence (Belay *et al.*, 1988; Huynh *et al.*, 2015; Nguyen-Hieu *et al.*, 2013; Wilson, 2018).

Periodontal disease begins with gingivitis and progresses to chronic periodontitis, affecting the periodontium. This inflammatory disease has a polymicrobial origin and typically arises from immunosuppressive conditions (Manosha, 2020). Poor oral hygiene, smoking, betel chewing with or without tobacco, genetic susceptibility, poor nutrition, age and immunosuppression of patients due to diabetes, pregnancy related hormonal changes, HIV infection are among the leading risk/predisposing factors of multifactorial entity 0f the commonest chronic inflammatory disease of elderly can lead to tooth loss if not treated (Manosha, 2020). These factors act individually or synergistically to cause microbial dysbiosis in periodontal pockets and supra gingival plaque providing an opportunity to elevate pathobiont which are putative periodontal pathogens avoiding immune surveillance and immune elimination (Perera and Perera, 2020; Seneviratne *et al.*, 2011).

The interactions among a consortium of microbes in polymicrobial infections involve cooperation/synergism and competition/antagonism. Recent advancements in Next-Generation Sequencing (NGS) technologies, especially over the past decade (Perera *et al.*, 2016), have opened up new ways to explore the diversity of microbial communities in unprecedented detail. As a result, hypothetical models have been proposed to explain the progression of periodontal disease, highlighting the virulence factors of low-abundance microbial species in these infections. These species can work synergistically with more prevalent genera, a phenomenon referred to as polymicrobial synergy (Manosha, 2020; Lamont and Hajishengallis, 2015; Hajishengallis *et al.*, 2012), which contributes to chronic inflammation in the oral cavity. It is reasonable to consider the potential role of minority archaea in the development of periodontal disease alongside established periodontal pathogens.

The keystone pathogen hypothesis addresses previous arguments by identifying specific low—abundance microbial pathogens that have a disproportionately large impact on their communities. In the context of microbial literature, the term "keystone" refers to species that play a critical role in maintaining the structure (Manosha, 2020; Lamont and Hajishengallis, 2015; Hajishengallis *et al.*, 2012) of their communities despite their low abundance. This hypothesis suggests that some of these low-abundance pathogens can trigger inflammatory diseases by altering the composition of polymicrobial communities (Manosha, 2020). Therefore, it is reasonable to assume that low-abundance archaea may facilitate the succession of orange and red complex periodontal pathogens as periodontal disease progresses (Socransky *et al.*, 1998). Recent advancements in biofilm technologies have improved our understanding of the ecological processes involved in the assembly succession of the periodontal community (Manosha, 2020).Undisturbed plaque accumulation experiment has revealed that the yellow complex facultative anaerobes such as *Streptococcus intermedius*, *Streptococcus oralis*, and *Streptococcus mitis* were increased in numbers and proportions (Manosha, 2020). Subsequently, the purple complex member–*Veillonella parvula*, green complex member-*Capnocytophaga gingivalis* as well as an orange complex member-*Fusobacterium nucleatum* during 7-days of supra gingival biofilm regrowth, in the same experiment (Teles *et al.*, 2012; Uzel *et al.*, 2011). At last, the red complex pathobionts *Porphyromonas gingivalis*, *Tannerella forsythia,* and *Treponema denticola* were established in the supra gingival plaque to finish the landscape

of periodontal disease (Teles *et al.*, 2012; Uzel *et al.*, 2011). Transition from facultative anaerobes to strict anaerobes was evident in the progression of periodontitis, thus it is reasonable to assume that the hypoxic environment in the supra gingival biofilm is ideal for the colonization of strict anaerobes at the final stage of supra gingival biofilm (Manosha, 2020). There is a paucity of information on the role of methanogenic archaea in the progression of periodontal disease. The cooperation of methanogens in the syntrophic growth of co-habitants in the periodontal pockets is important to note that methanogens can form methane independently from H_2 by using other electron donors, such as methanol, methylamine, acetate, ethanol, or formiate help other fermenting pathogens by through interspecies hydrogen transfer, is possible. It is reasonable to assume that the H_2 consumption linked with the syntrophic growth of Volatile Fatty Acid (VFA) occurs within the complex oral plaque consortium (Horz and Conrads, 2011).

Methanogens were especially detected at site of poly-microbial anaerobic biofilms in the periodontal pockets as the metabolic compatibility may contribute for the progression of periodontal diseases are initiated and progressed by at or below the gingival margin. Here we can assume that they support the growth of fermenting bacteria, which themselves are opportunistic pathogens.

Virulent attributes of these microbes are termed as 'poly microbial synergy' involving concerted action, which could progress the disease condition via chronic inflammation (Manosha, 2020). There is an involvement of methanogens in the overall infectious process with interspecies hydrogen transfer being an indirect mechanism of virulence (Lepp *et al.*, 2004). In a study conducted to investigate the diversity of *Archaea* in the human sub gingival crevice, SSU rDNA was amplified with domain-specific primers and cloned independently from samples collected from six patients with periodontitis, it has been revealed that the relative abundance of archaea increased with the severity of periodontal disease. Moreover, there was a corresponding decrease in the relative abundance of SSU rDNA coinciding with an improvement in periodontal status after treatment (Lepp *et al.*, 2004). A study compared the number of methanogens to the occurrence and abundance of ten bacterial species. These species include Tannerella forsythia, *Porphyromonas gingivalis*, and *Treponema denticola*, which together form the "red complex." Additionally, the study examined *Campylobacter rectus*, *Fusobacterium nucleatum*, *Parvimonas micra*, and *Prevotella intermedia*, among others, which are members of the "orange complex." Other species evaluated were *Aggregatibacter actinomycetemcomitans*, *Eikenella corrodens*, and *Actinomyces viscosus*. The findings suggest that the metabolic activity of methanogens supports the bacterial communities associated with both the red and orange complexes in cases of human periodontitis. This influence is likely mediated through direct or indirect interactions with *P. intermedia*. The study also involved defined mixtures of co-cultures that included methanogens combined with either *P. intermedia*, *T. forsythia*, *or P. gingivalis*, observing the resulting growth (Horz and Conrads, 2011). Dental plaque specimens were cultured in an anoxic liquid medium designed for methanogens, along with negative control tubes, as conducted by Huynh and colleagues in 2015 (Huynh *et al.*, 2015). In their study, methanogens were detected in 1 out of 15 (6.67%) control samples and 36 out of 65 (55.38%) samples from patients with periodontitis ($p < 0.001$). Specifically, *Methanobrevibacter oralis* was identified in one control and thirty-one patient samples, while *Methanobrevibacter smithii* was found in two patients. Additionally, a potential new species, *Methanobrevibacter* sp. strain N13, was detected in three patients with severe periodontitis (Huynh *et al.*, 2015). In a separate study aimed at assessing the prevalence of archaea among chronic periodontitis patients in India (Ashok *et al.*, 2013), the research found that the prevalence of archaea was 29.4% in chronic periodontitis patients, compared to 11.8% in healthy subjects. This difference was not statistically significant. However, when examining the prevalence of archaea in different periodontal conditions, it was found that the prevalence in deep periodontal pockets was 47.1%, and in shallow pockets, it was 11.8%. In healthy sulci, it was 12.5%. These results indicate a statistically significant difference between the prevalence of archaea in deep periodontal pockets (47.1%) and healthy sulci (12.5%), as well as between deep periodontal pockets (47.1%) and shallow pockets (11.8%) (Ashok *et al.*, 2013).

Researchers are investigating the outcome of interaction between archaea and orange and red complex members in the land scape of periodontal disease and it is hypothesized that under anoxic conditions methanogens would remove end-products, lowering the concentration of H_2 and possibly encouraging fermenters especially the putative periodontal pathogens. The Sulphate Reducing Bacteria (SRB) seem competitors of methanogens in most environments due to the usage of sulphate as electron acceptor. This

justifies the previous observations of increased proportions of *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* in the absence of methanogenic archaea ((Lepp *et al.*, 2004; Matarazzo *et al.*, 2012). Methanogenic archaea belong to the Sulphate Reducing Bacteria (SRB), a diverse group of prokaryotic that share the capability of using sulphate or other oxidized sulfur compounds as a terminal electron acceptor in the oxidation of organic matter and archaea are also responsible for the production of Volatile Sulfur Compounds (VSCs) are primarily responsible for oral malodor (Nakano *et al.*, 2002). Therefore, it is important to incorporate the role of methanogenic archaea in the landscape of periodontal disease for the comprehensiveness of the ecological succession.

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Cite this article as: Manosha Lakmali Perera and Irosha Rukmali Perera (2025). Reemerging importance of methanogenic archaea in the landscape of periodontal disease. *African Research Journal of Medical Sciences.* 2(2), 77-81. doi: 10.62587/AFRJMS.2.2.2025.77-81.