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Review Article

Inflammaging and Immunosenescence: The New Biological Paradigm of Periodontal Disease in Older Adults. Narrative Review

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Abstract

Periodontitis has long been described as a chronic inflammatory disease driven by the interaction between a dysbiotic biofilm and an altered host immune response. This model, however, does not fully explain the greater susceptibility, faster progression and poorer treatment response observed in older adults. From a geroscience perspective, biological aging itself reshapes the periodontal environment through inflammaging and immunosenescence, contributing to loss of periodontal homeostasis beyond microbial dysbiosis alone. The aim of this narrative review was to examine how inflammaging, immunosenescence, oral microbiome aging and declining regenerative capacity converge to influence periodontal disease in older adults and to consider how this biological understanding may be translated into clinical practice. Literature indexed in PubMed and Google Scholar and published between 2021 and 2026 was reviewed, supplemented by earlier foundational work. Four interconnected mechanisms emerged. Cellular senescence and the senescence-associated secretory phenotype sustain chronic inflammation, matrix degradation and alveolar bone loss. Immunosenescence impairs neutrophil chemotaxis and antimicrobial function while permitting excessive inflammatory activation. Age-related microbiome remodeling reduces bacterial diversity and favors periodontal pathogens, sustaining cytokine production. Declining periodontal ligament stem cell proliferation and differentiation limit the response to regenerative therapy. These processes reinforce one another in a feed-forward loop, so that aging acts as an active determinant of disease susceptibility, progression and therapeutic outcome rather than a passive background variable. Precision periodontal medicine, integrating genetic, multi-omic and biosensor-based profiling, offers a translational framework for individualized risk assessment, earlier diagnosis and targeted treatment in an increasingly aging population.

Keywords: Periodontitis; Aging; Immunosenescence; Inflammaging; Oral Microbiome; Regenerative Medicine; Precision Medicine; Biomarkers

Introduction

Periodontitis is a chronic inflammatory disease characterized by progressive destruction of the tooth-supporting tissues and its prevalence and severity increase with age [1]. Although it has traditionally been explained through the interaction between a dysbiotic biofilm and an altered immune response, this model does not fully account for the greater progression and

susceptibility observed in older people. From a geroscience perspective, periodontitis is now recognized as a condition influenced by biological aging, in which processes such as inflammaging and immunosenescence contribute to compromised immune regulation and loss of periodontal homeostasis [1,2].

Biological aging involves the progressive accumulation of cellular and molecular modifications that affect tissue function and increase the risk of chronic diseases [3,4]. Alongside the hallmarks of aging, cellular senescence has emerged as an important mechanism of age-related decline. It is characterized by a stable cell-cycle arrest in which cells remain metabolically active but lose their proliferative capacity [3]. While transient senescence plays physiological roles in tissue repair and remodeling, the persistent accumulation of senescent cells promotes a pro-inflammatory environment through release of the Senescence-Associated Secretory Phenotype (SASP), which includes cytokines, chemokines and other mediators capable of disrupting tissue homeostasis [5].

Rationale

Two observations motivate the present review. First, the conventional biofilm-host model predicts that periodontal destruction should track microbial burden, yet experimental gingivitis studies show that older adults develop more severe inflammation than younger adults despite accumulating comparable amounts of plaque, which indicates that the host response rather than the bacterial challenge accounts for the age-related difference [1]. Second, regenerative and reconstructive therapies that perform predictably in younger patients yield slower and less consistent outcomes in older patients, even when the biomaterial and surgical technique are identical, which points to a change in the biological competence of the host tissue rather than a deficiency of the intervention [6]. Neither observation is explained by dysbiosis alone. Both are explained if biological aging is treated as an active determinant of periodontal outcome and this reframing carries direct consequences for how clinicians assess risk, time their interventions and set expectations with older patients.

Age-related mechanisms are also active within periodontal tissues. Because the periodontium is constantly exposed to microbial biofilms, mechanical forces and inflammatory responses, it may be particularly susceptible to the accumulation of cellular damage and to disruption of tissue homeostasis [5]. Recent studies have reported increased expression of senescence markers and SASP-related inflammatory mediators in periodontal tissues affected by periodontitis, suggesting that cellular senescence is not only a consequence of aging but also an active mechanism of periodontal destruction [7,8]. The persistence of senescent cells may promote chronic inflammation, extracellular matrix degradation, impaired tissue repair and alveolar bone loss, contributing to progressive periodontal breakdown [5,7].

Although microbial dysbiosis remains a central factor in the development of periodontitis, current evidence indicates that aging-related processes, particularly inflammaging and immunosenescence, are important determinants of disease susceptibility and progression in older adults [1,6]. Incorporating these mechanisms into the traditional understanding of periodontitis provides a broader biological perspective in which periodontal disease results from the interaction among the microbiome, biological aging and host immune responses [8,9]. The way these aging processes converge on periodontal breakdown is depicted in Fig. 1.

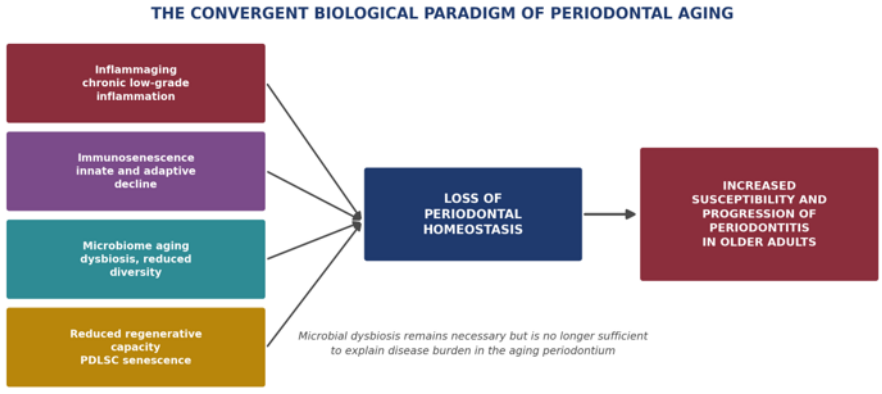

Figure 1: The convergent biological paradigm of periodontal aging.

Aim, Objectives and Methods

The aim of this narrative review was to examine current evidence on the role of inflammaging and immunosenescence in periodontal disease and their contribution to an emerging biological paradigm of periodontitis in older adults. The specific objectives were to summarize the hallmarks of biological aging relevant to the periodontium, to analyze immunosenescence and inflammaging as mechanisms of periodontal breakdown, to describe age-related remodeling of the oral microbiome, to evaluate how aging constrains regenerative therapy and to appraise the translational potential of precision periodontal medicine. Literature indexed in PubMed and Google Scholar and published between 2021 and 2026 was reviewed, supplemented by earlier foundational work where conceptually necessary. Given the narrative design, no formal quality-scoring protocol or quantitative synthesis was applied.

Biological Aging and the Periodontium

Biological aging is not synonymous with the passage of time. It describes the progressive accumulation of molecular and cellular damage that erodes tissue function and raises susceptibility to chronic disease and it proceeds at different rates in different individuals [3,4]. This distinction is clinically important, because two patients of the same chronological age may differ substantially in immune competence, regenerative capacity and inflammatory tone. Analyses combining national survey data with Mendelian randomization have shown that measures of biological aging are associated with periodontitis independently of chronological age, supporting a causal rather than merely correlative relationship [10].

Several interrelated hallmarks of aging are directly relevant to periodontal tissue. Cellular senescence produces a stable cell-cycle arrest in which cells remain metabolically active and secrete the SASP [3]. Chronic low-grade systemic inflammation or inflammaging, raises circulating concentrations of Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-alpha) and C-reactive protein even in otherwise healthy older adults [4]. Immunosenescence progressively degrades both innate and adaptive immune function [11]. Alongside these, the oral microbial community is itself remodeled with age and the regenerative reserve of the periodontal ligament declines [12,13]. Experimental work has shown that bacterial lipopolysaccharide can induce premature osteocyte senescence, providing a mechanistic link between the microbial challenge and the aging phenotype within alveolar bone itself [2]. The principal aging mechanisms acting on the periodontium and their tissue-level effects are summarized in Table 1.

Mechanism	Key features	Effect on the periodontium	Reference
Cellular senescence and SASP	Stable cell-cycle arrest; senescence-associated secretory phenotype (cytokines, chemokines)	Chronic inflammation, matrix degradation, impaired repair, alveolar bone loss	[3,5]
Inflammaging	Chronic low-grade systemic inflammation; raised IL-6, TNF-alpha, CRP	Exaggerated host response and accelerated tissue destruction	[4,8]
Immunosenescence	Thymic involution; accumulation of senescent immune cells; innate and adaptive decline	Impaired pathogen control and disrupted periodontal homeostasis	[9,11]
Neutrophil dysfunction	Reduced chemotaxis and antimicrobial function; excessive activation	Ineffective microbial control and unresolved inflammation	[14,15]
Microbiome aging	Reduced diversity; shift toward periodontal pathogens (dysbiosis)	Sustained cytokine production and low-grade inflammation	[12,16]
Reduced regenerative capacity	Declining PDLSC proliferation, differentiation and self-renewal	Slower, less predictable repair and weaker response to regenerative therapy	[13,17]

Table 1: The principal aging mechanisms acting on the periodontium and their tissue-level effects.

Immunosenescence

Aging has been correlated with a greater propensity to develop periodontal diseases [14,18]. Chronological age is nevertheless not the only factor to consider, since biological changes have more recently been shown to influence periodontal disease as well [10].

Immunosenescence can be described as the set of changes that progressively impair the response of the immune system with advancing age [7]. Its characteristic features include thymic involution, inflammaging and the accumulation of senescent immune cells [11]. Immunosenescence affects both innate and adaptive immunity and disturbs periodontal homeostasis [9]. Senescent cells warrant separate consideration, because although they do not follow an identical biological process, they exert a broad influence on immune and inflammatory responses, which in turn affects periodontal disease [19,20]. The principal steps of this cascade are outlined in Fig. 2.

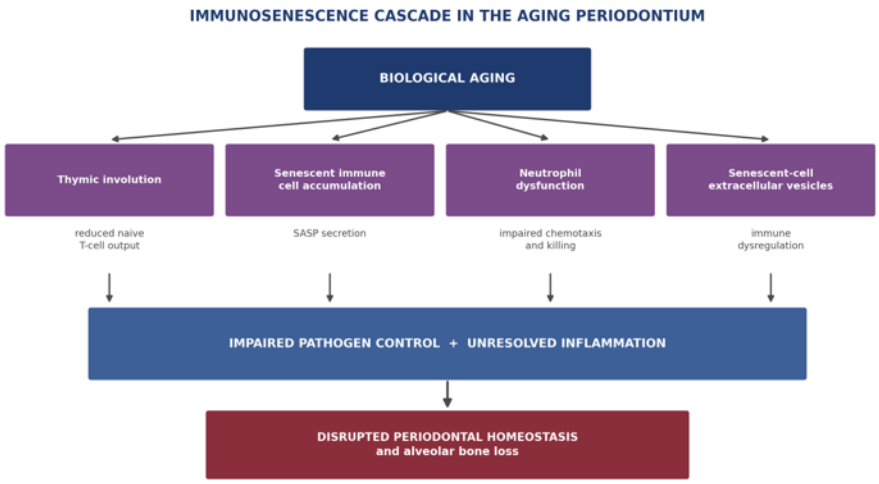

Figure 2: Immunosenescence cascade in the aging periodontium.

Immunosenescence affects general health as well as oral health [7]. With respect to the aging periodontium, its effect on the neutrophil deserves particular emphasis, since this cell is among the most important effectors of innate immunity. With advancing age, neutrophil antimicrobial function diminishes, inflammatory activation becomes excessive and chemotaxis declines, which alters immune competence and periodontal health [14,19]. Neutrophils are central to the periodontal pocket environment, where their dysregulated activation contributes directly to tissue destruction rather than resolution [15]. Current data also show that extracellular vesicles derived from senescent cells drive immune dysregulation and contribute to chronic inflammatory reactions [19].

Taken together, these biological mechanisms reduce regenerative and protective capacity, resulting in a loss of bone homeostasis that affects periodontal tissue in older adults [9]. Immunosenescence and bone homeostasis are mechanistically linked and this relationship has been proposed as a therapeutic target in age-related skeletal disorders more broadly [11]. These interactions foster an environment of continuous inflammation with a direct impact on periodontal health [8]. Collectively, they contribute to the induction of inflammaging, which is explored in the following section [7,21].

Inflammaging

Inflammation is the natural defense of the body against injury, infection and harmful microorganisms. Under normal conditions it protects tissues and promotes healing; when it becomes chronic, however, it can damage healthy tissues and contribute to diseases such as cardiovascular disease, diabetes, cancer and periodontal disease [10,22]. As people age, the immune system undergoes changes that produce a persistent, low-grade inflammatory state known as inflammaging, a term first introduced by Franceschi and colleagues in 2000 to describe the gradual increase in pro-inflammatory activity associated with aging [20].

Inflammaging is characterized by elevated levels of inflammatory mediators, including IL-6, TNF-alpha and C-reactive protein, even in otherwise healthy older adults [8]. Aging is also accompanied by immunosenescence, the gradual decline in immune function and by cellular senescence, in which damaged cells stop dividing but continue releasing pro-inflammatory molecules [7,21]. Together, these processes sustain chronic systemic inflammation and increase the risk of age-related diseases [4].

Periodontal disease is among the conditions most strongly associated with inflammaging. It develops when the host inflammatory response to dental plaque bacteria becomes excessive or dysregulated, destroying the supporting tissues around the teeth [8]. Because older adults already experience a heightened inflammatory state, they are more susceptible to an exaggerated immune response that accelerates periodontal tissue destruction [21,23]. Inflammaging has been described as a driver of both alveolar bone loss and impaired repair, which explains why the same inflammatory environment that destroys tissue also limits its restoration [23].

Evidence for this relationship comes from experimental gingivitis studies comparing younger and older adults. Although both groups accumulated similar amounts of dental plaque after temporarily discontinuing oral hygiene, older participants developed significantly more severe gingival inflammation. This finding suggests that aging alters the immune response rather than increasing bacterial accumulation and that periodontal tissues consequently become more vulnerable to damage [1,21].

Inflammaging is therefore now recognized as an important biological mechanism linking aging to periodontal disease [6]. Together with immunosenescence and cellular senescence, it creates a chronic inflammatory environment that weakens immune regulation and promotes tissue destruction. Understanding these processes may help researchers develop therapies that target chronic inflammation, improve periodontal health and enhance overall health outcomes in older adults [7,21].

Microbiome Aging

The oral microbiome is a complex, dynamic community of bacteria, fungi, viruses and archaea that plays a fundamental role in maintaining oral health by supporting tissue homeostasis, mucosal immunity and protection against pathogens [24]. Microbiome aging refers to the progressive remodeling in the composition and function of this community that occurs throughout life. Current evidence suggests a bidirectional relationship in which aging reshapes the oral microbiome while these microbial alterations, in turn, may influence the aging process and increase susceptibility to age-related diseases [16]. Although this interaction is increasingly recognized, a distinct age-related microbial signature has not yet been fully established, because the oral microbiome is shaped by multiple biological and environmental factors [12].

Rather than undergoing complete disruption, the oral microbiome experiences a gradual reorganization with aging. Older adults tend to show reduced bacterial richness and alpha diversity, resulting in a less diverse ecosystem, along with shifts in the relative abundance of specific genera such as Rothia, Neisseria, Mycoplasma and Streptococcus [12,16]. Because frailty, oral function and dentition status also help shape the aging oral microbiome, chronological age alone does not fully explain these changes [21]. Collectively, such alterations may reduce ecosystem stability, favor dysbiosis and increase the risk of oral and systemic disease in older adults [16].

As the oral microbiome changes with age, beneficial bacteria decrease while periodontal pathogens become more abundant [16]. This imbalance promotes continuous production of inflammatory cytokines, including interleukin-1 beta, IL-6 and TNF-alpha, leading to a persistent low-grade inflammatory state that contributes to periodontal disease progression and to the low-grade inflammation commonly observed in older adults [8,16].

Age-related microbial alterations occur alongside a gradual decline in immune function, which makes it more difficult for the host to maintain a balanced microbial community and allows periodontal pathogens to become more prevalent [9]. At the same time, these microorganisms continuously stimulate the immune system, creating a persistent inflammatory response that contributes to periodontal tissue damage [15,16].

Recent studies suggest that this process is driven not only by changes in the microbiome but also by age-related immune dysregulation [19]. Immune cells, particularly neutrophils, become less effective at controlling the microbial challenge and resolving inflammation [14,15]. As a result, microbiome aging and immunosenescence reinforce each other, promoting chronic

inflammation and increasing susceptibility to periodontitis in older adults [9,23]. This self-reinforcing relationship is illustrated in Fig. 3.

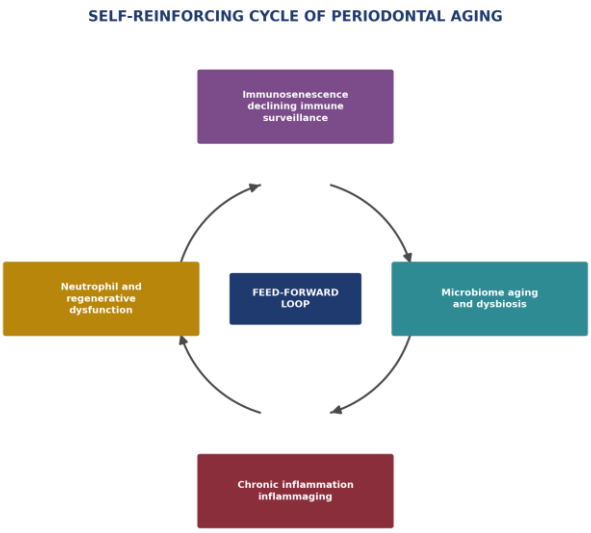

Figure 3: Self-reinforcing cycle of periodontal aging.

These microbial changes carry important implications for periodontal health. As the community gradually shifts toward dysbiosis, beneficial bacteria decline while periodontal pathogens expand, creating an environment that favors chronic inflammation and disease [16]. Notably, such changes may appear before clinical signs of periodontitis become evident, suggesting that the oral microbiome could help identify older adults at higher risk of developing the disease [24].

Periodontitis is a complex disease driven by the interaction among microbial dysbiosis, chronic inflammation and the host immune response [23,24]. Recent work indicates that its progression is influenced not only by dysbiosis but also by oxidative stress and immune dysregulation. Future therapies therefore aim not only to control the bacterial biofilm but also to restore microbial balance and target the biological processes involved in disease progression [25].

One consequence of this broader mechanistic picture is that treatment need not be confined to biofilm removal. If oxidative stress and dysregulated host immunity contribute independently to progression, then agents that modulate these pathways become legitimate adjuncts rather than speculative additions and their value would be expected to be greatest in older patients in whom the underlying inflammatory tone is already elevated [25]. A second consequence concerns direction of benefit. Because periodontal inflammation contributes measurably to systemic inflammatory burden and because that burden is itself implicated in cardiovascular risk, periodontal treatment in older adults may be understood as an intervention with reach beyond the oral cavity [22]. Framed this way, maintaining periodontal health becomes one component of a wider strategy for healthy aging rather than an isolated dental objective.

Regenerative Limitations: Stem Cells, Platelet Concentrates and Growth Factors

The alterations in the periodontal microenvironment associated with aging directly affect the regenerative capacity of periodontal tissues and the progression of periodontal disease [23]. In this context, stem cell-based therapies, platelet concentrates and growth factors have shown considerable value [26]; however, their efficacy may be reduced in older patients because of the biological changes associated with aging itself [13]. The relationship between therapeutic input and host biological competence is summarized in Fig. 4.

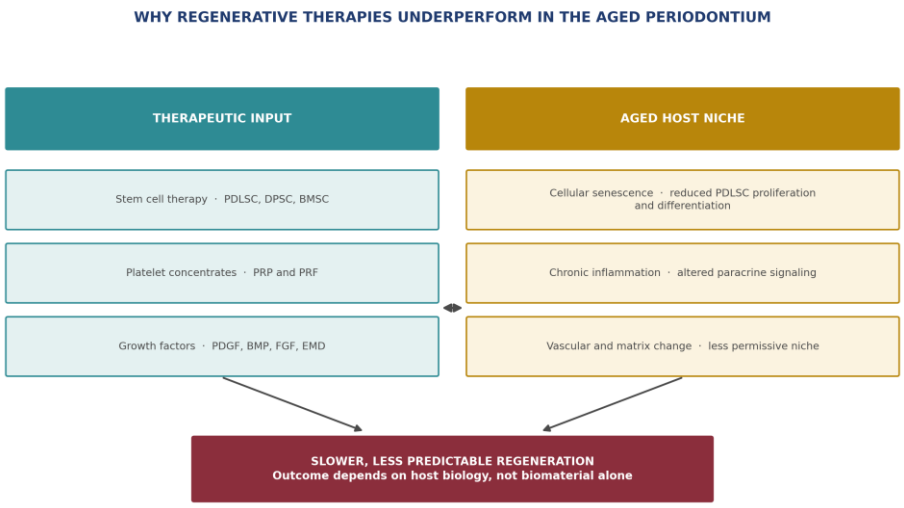

Figure 4: Why regenerative therapies underperform in the aged periodontium.

Aged periodontal tissue has a reduced regenerative capacity because aging causes functional deterioration of cells [13,28]. Over time, periodontal ligament stem cells show decreased proliferation, osteogenic differentiation and self-renewal, together with increased cellular senescence and accumulated cell damage [17,29]. Mechanistic work indicates that impaired mitophagy contributes to the reduced tension-driven osteogenic differentiation of these cells during ageing, offering one explanation for why mechanically stimulated repair becomes less effective in older tissue [17]. As a consequence, tissue repair becomes slower and incomplete and factors such as chronic inflammation, vascular alterations, changes in the extracellular matrix and altered molecular signaling create a less favorable niche for regeneration [27].

Stem cells play a fundamental role in regeneration, as they restore periodontal tissues through proliferation, migration to sites of injury and differentiation into cell types such as osteoblasts, cementoblasts and fibroblasts [29]. Periodontal ligament stem cells are more specific to periodontal regeneration, whereas dental pulp and bone marrow stem cells show marked osteogenic potential and secrete paracrine factors that favor new blood vessel formation, modulate inflammation and stimulate repair [27,30]. Aging, however, alters these processes by inducing cellular senescence and reducing proliferation, migration and differentiation, so that stem cells lose much of their capacity to respond to regenerative stimuli, translating into slower healing and less predictable clinical results in older patients [13,29].

Platelet concentrates, including platelet-rich plasma and platelet-rich fibrin, can enhance periodontal regeneration by sustainably releasing growth factors that favor angiogenesis, soft-tissue healing and bone formation [26]. Nevertheless, variability in clinical preparation protocols and heterogeneity in patient selection make results inconsistent. Aging further limits platelet function and cellular responsiveness, reducing the regenerative response even when the concentrate delivers adequate biological signals; transcriptomic and proteomic analyses of senescent platelets support this interpretation [31].

Growth factors such as platelet-derived growth factor, bone morphogenetic proteins, fibroblast growth factor and enamel matrix derivative are among the most widely used to stimulate bone formation, increasing proliferation of osteoprogenitors, stimulating angiogenesis and enhancing osteoblast differentiation [26,30]. Their effectiveness depends on a biologically competent microenvironment. Because aging reduces proliferative capacity and alters paracrine communication, clinical success is limited, since the outcome depends not only on the biomaterial used but also on the capacity of the host for regeneration [13,28].

Regenerative therapies in periodontal treatment therefore offer considerable promise, yet the biological and functional changes associated with aging remain a key limitation [13,27]. Recognizing this constraint allows a more accurate interpretation of the variability observed in clinical outcomes and supports the design of individualized therapeutic strategies matched to the biological competence of the patient rather than to chronological age alone [28,29]. Importantly, this limitation should not be read as a contraindication. Population-level data indicate that older age by itself does not preclude successful periodontal or peri-implant therapy and that appropriately selected older patients respond favorably to treatment [18].

Precision Periodontal Medicine: Diagnostic and Therapeutic Translation

The mechanisms described in the preceding sections acquire clinical value only when they can be measured in an individual patient and acted upon. Precision periodontal medicine provides this translational framework, using genetic, multi-omic, microbiological and biosensor-based profiling to stratify risk, detect disease earlier and target treatment [32]. The principal biomarkers and tools relevant to periodontal aging are summarized in Table 2 and the translational pathway is outlined in Fig. 5.

Category	Example or target	Application	Reference
Genetic polymorphisms	IL-1, IL-6, TNF-alpha, FPR1	Susceptibility risk stratification for periodontitis and peri-implantitis	[32,33]
Multi-omics integration	GWAS, single-cell and spatial transcriptomics, Mendelian randomization; GNLY	Causal gene discovery and therapeutic drug prediction	[34]
Shared inflammatory genes	CD79A, CXCL13, SLAMF7, CCL18	Oral-systemic links between periodontitis and rheumatoid arthritis	[35]
Salivary and breath biosensors	Volatile sulfur compounds; H2S from Porphyromonas gingivalis	Non-invasive, point-of-care diagnosis	[36,37]
Personalized antibiotic selection	Subgingival biofilm culture-guided therapy	Greater pathogen reduction than standard protocols	[38]
Host-modulation targets	Oxidative stress and immune dysregulation pathways	Adjunctive control of progression beyond biofilm removal	[25]

Table 2: Translational pathway.

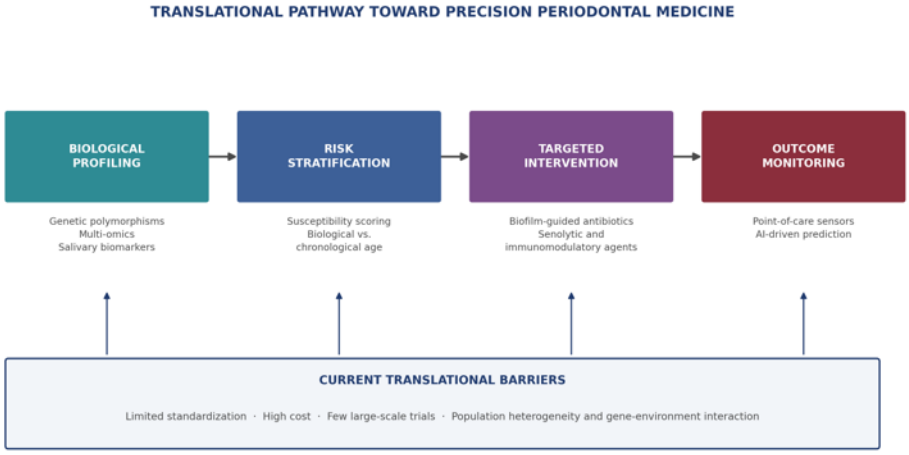

Figure 5: Translational pathway towards precision periodontal medicine.

In the domain of biomarkers, polymorphisms in IL-1, IL-6, TNF-alpha and FPR1 are associated with increased susceptibility to periodontitis and peri-implantitis, although their utility in isolation is limited by population heterogeneity and gene-environment interactions [33]. Genetic testing in periodontitis therefore remains an adjunct to, rather than a replacement for, clinical assessment [32]. Multi-omic integration has identified causal genes such as GNLY in monocytes and natural killer cells, linking periodontal tissue to systemic comorbidities and generating candidate therapeutic targets [34]. Genes shared between chronic periodontitis and rheumatoid arthritis, including CD79A, CXCL13, SLAMF7 and CCL18, reinforce the oral-systemic inflammatory link and point to further therapeutic possibilities [35]. Nanomaterial-based biosensors detect salivary and breath

volatile sulfur compounds associated with Porphyromonas gingivalis with high sensitivity and have already been tested in patients, offering portable and affordable point-of-care diagnosis [36,37].

In the domain of treatment, a randomized clinical trial in which antibiotic selection was guided by the subgingival biofilm of each patient altered treatment in more than 80% of cases and produced a greater reduction in periodontal pathogens than standard protocols [38]. Combining biofilm-guided therapy with computationally predicted, genetically targeted drug selection supports a genuinely individualized approach [34]. Interventions directed at oxidative stress and host immune dysregulation represent a complementary strategy that addresses the aging phenotype rather than the microbial challenge alone [25]. Key barriers nevertheless remain, including limited standardization of assays and thresholds, high cost and a scarcity of large-scale trials in older populations [32].

Conclusion

Periodontal disease in older adults is not adequately explained by microbial dysbiosis acting on a static host. Immunosenescence, inflammaging, age-related microbiome remodeling and declining regenerative capacity operate together in a self-reinforcing loop, so that biological aging functions as an active determinant of susceptibility, progression and treatment response. This reframing has three practical consequences. Risk assessment in older patients should account for biological rather than chronological age. Expectations for regenerative therapy should be calibrated to host biological competence, while recognizing that age alone is not a contraindication to treatment and periodontal care should be positioned within a broader strategy for healthy aging, given the contribution of periodontal inflammation to systemic inflammatory burden. Precision periodontal medicine offers a credible route from these mechanisms to individualized care, although standardization, cost and the limited number of large-scale trials remain substantial obstacles to routine implementation.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

This manuscript is a narrative literature review and did not involve human participants, animal subjects or patient data. No ethical approval was required.

Informed Consent Statement

Not applicable.

Authors' Contributions

All authors contributed equally to this paper.

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