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Healthy aging: when periodontal health matters

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Providing care for the elderly has been considered a significant challenge for modern medicine. As age progresses, diseases become more frequent and severe than those observed at a younger age. This is particularly relevant for infectious diseases, typical in the elderly and usually associated with poor outcomes. Moreover, when persisting and diffusing into the bloodstream (i.e. bacteremia), these infections keep up with the demand for immune cells' response and consequently increase the concentration of inflammatory markers systemically. This phenomenon is known as "inflammaging", which potentially triggers or facilitates the development and progression of several age-related disorders, such as cancer, cardiovascular and neurodegenerative diseases. Periodontal disease is one of the most prominent among the disparate number of causal factors responsible for bacteremia and low-grade systemic inflammation in the aging population. This inflammatory disorder is triggered by a dysbiosis of certain bacterial species that activates a massive local toxic deleterious immune response leading to non-reversible damage of supportive tissues surrounding the teeth. In chronic, oral pathogens and their toxic factors can penetrate the bloodstream contributing to systemic inflammation. Based on this premise, it seems evident that maintaining oral health in the elderly is vital not just for owning healthy mouth but also because it contributes to a healthy aging. This review provides an updated account of molecular insights into the bidirectional association between oral health and "successful" aging.

Key words: periodontitis, immunosenescence, inflammaging, aging, oral health

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INTRODUCTION

In the last century, the portion of older adults globally has increased rapidly, with the number of people aged over 60 years old reaching almost 22% in 2050 [1]. Of course, prolonged life expectancy is associated with an augmented risk of chronic degenerative disorders frequently observed in older populations, with national healthcare systems facing this evolution

with enormous costs [2-4]. According to Franceschi et al. [5], centenarians representing a model of "successful" or healthy aging usually exhibit medical histories with remarkably low incidence rates of common age-related disorders such as cardiovascular-related diseases (CVDs), diabetes, Parkinson's and Alzheimer's disease, and cancer [4,5]. Thus, great interest has been raised in understandingthe molecular basis of successful aging and identifyinga potential strategy to achieve it. What differentiates the unsuccessful aging process from a successful one is undoubtedly a different response to a condition known as "inflammaging". This low-grade chronic inflammatory process, resulting from the long-term stimulation of the innate immune system, contributes to the onset of age-related pathologies. In contrast, in subjects who age successfully (with no comorbidities), like centenarians, it has been suggested that this inflammatory status is counterbalanced by anti-inflammaging mechanisms [6-9]. Of note, several are the cellular and molecular mechanisms involved in inflammaging, and among these, dysbiosis (an imbalance in the host-microbial community) appears to play a pivotal role [6,10]. This phenomenon is facilitated by physiologic and pathophysiologic changes occurring with aging, like an impairment in immune system functionality (immunosenescence) that enable host-microbiome alteration and contribute to the incidence and severity of infections, such as periodontitis [11-13]. Global data indicate that these oral disorders are highly prevalent among older adults (60 years and older), and due to their infective and inflammatory nature, they represent a significant public health issue in aging populations [14-17]. For instance, recent studies depicted a catastrophic situation with 68% of adults ≥ 65 years of age affected with chronic periodontitis in the USA [18,19]. In addition, several experimental and clinical data demonstrated that various age-related systemic diseases are strictly associated (in a bidirectional manner) with periodontitis [20,21]. Hence, it is more than plausible to speculate that controlling the development and progression of such oral disease may significantly decelerate biological aging [22].

Herein, in this Review, we discuss how periodontitis influences overall health status, representing a causal risk factor of accelerated aging. In particular, we mainly focused on the strict causal relationship between immunosenescence and periodontal disease and the consequent related effects on the development and progression of age-related disorders.

IMMUNOSENESCENCE AND INFLAMMAGING

Biologically, aging is associated with a physiological process of tissue degeneration related to chronic low-grade systemic inflammation [6,23,24] is characterized by high circulating cytokine levels such as tumor necrosis factor α (TNF), interleukin (IL)-6 and IL-1, and anti-inflammatory mediators, including the IL-1 receptor antagonist, and the soluble TNF receptors 1 and 2, despite the absence of general pathophysiological stress or infection [25,26]. This condition, known as inflammaging, has been associated with accelerated aging and age-related disorders that increase morbidity and mortality in the elderly population [27,28]. Among the numerous processes implicated in inflammaging, immunosenescence is for sure one of the most significant pathological drivers [29]. The existence of this process involves both cells of adaptative immunity like T and B cells and those of innate immunity, including natural killer (NK), neuthrophils, monocytes and macrophages.

T-cells

T-cells are involved in adaptive immunity and are critical for generating and maintaining long-term immunological memory and protection [30,31]. These cells direct robust humoral immunity (CD4+ T cells) and mediate cytotoxic responses (CD8+ T cells). However, as age progresses, some well-established defects in these populations of T-cells occur [30,31]. For instance, as demonstrated by Cho, with increasing age, hematopoietic stem cells (HSCs), have a decreased capacity to produce lymphoid progenitors (T, B, and NK cells) and are more prone to generate myeloid progenitors (megakaryocytes, erythroid, myeloid and some dendritic cells) [32]. Consequently, the HSCs are more prone to generate myeloid progenitors (megakaryocytes, erythroid, myeloid, and some dendritic cells) [32]. Moreover, in humans and mice, the involution of the thymus, a specialized central lymphoid organ located in the thorax, has been associated with a decreased output of naïve T cells [31]. As a result, circulating naïve T-cells undergo homeostatic proliferation into unprimed memory-like CD8 T cells, called "virtual memory" (VM) cells [33,34].

Further to these factors, significant evidence suggests that persistent latent infections (i.e. cytomegalovirus [CMV]) are associated with the deleterious modifications observed in the T-cell compartment with age [35,36]. Indeed, studies reveal that chronic CMV infection impacts the memory compartment and stimulates the expansion of CMV-specific memory CD8+ T-cells [37].

Altogether these mechanisms lead to a decreased response to infections and reduced vaccination efficiency in the older population. Most of these effects have been attributed to the age-associated loss in T cells of the CD28 molecule [38-41]. This costimulatory molecule interacts with ligands expressed on antigen-presenting cells (APCs), stimulating T-cell activation and proliferation [41]. From a functional standpoint, loss of CD28

leads to several upstream and downstream outcomes, including decreased ability to secrete IL-2, reduced T-cell repertoire diversity, decreased telomerase activity, proliferation, and survival upon antigen exposure [42-45]. Although the mechanisms responsible for the loss in CD28 with age are not fully comprehended, several studies suggest a potential implication for TNF-α. Indeed, this factor can significantly inhibit the expression of CD28, and its levels are increased in older adults with chronic inflammaging [46].

In addition, as demonstrated by Patrick et al., the downregulation of CD28, along with the reduced expression of CD27, is accompanied by the loss of human telomerase reverse transcriptase (hTERT), leading to a decreased telomerase activity and increased telomers frailty [47].

Of note, memory CD8+ T cells also acquire CD57, a glycoepitope well-recognized marker of replicative senescence [48], and as reported by Martínez-Zamudio et al. develop high levels of senescence-associated β-galactosidase (SA-βGal) activity [49].

B-Cells

B-cells are responsible for developing long-lasting protective antibody responses and immunological memory following infections or vaccination. Hence, a defect in the function of these cells negatively impacts their capacity to trigger a correct primary or secondary response [46,50]. B cell development depends on lymphoid-biased hematopoietic stem cells (HSC), which develop into pro-B cells, pre-B cells, and immature B cells in the bone marrow. Once they exit from the bone marrow, these immature cells complete their maturation. These mature cells are composed of two peripheral pools of follicular or marginal zone B cells [51]. Of note, total peripheral B cell count, which has been associated with impaired bone marrow production in the bone marrow, progressively decline with aging [52]. This phenomenon is at least in part dependent on the above-mentioned age-associated switching of HSCs from lymphoid- to myeloid-biased cells that lead to a reduction in both T and B-cells production [32].

In addition, as suggested by Stephan et al. [53,54] an altered function of bone marrow stromal cells (BMSCs) and pro-B cells impacts mature B-cells production. Indeed, BMSCs produce the IL-7, which is essential for the transition of pro-B into pre-B cells, and as demonstrated by these authors, BMSCs from aged mice produce less IL-7. In addition, pro-B-cells from aging mice appear less responsive to IL-7 signaling.

As demonstrated in aged mice, the residual pools of pro-B cells present lowered levels of the surrogate light chain (SLC) proteins λ5 and VpreB [55-57]. This effect overlaps with declines in the expression of E47/E2A [56,58-60] and Early B-cell factor (EBF) [61,62]. Both these factors regulate the SLC gene expression [63]. The reduction in SLC causes a loss of pre-B cell receptors (pre-BCR), restraining the expansion and development of pre-B cells and reducing the production of B cells with normal functions [57].

Moreover, the increased secretion of TNF-α by old follicular B cells [64] yields the apoptosis of SLC+ pro-B cells in the bone marrow, consequently leading to the accumulation of SLC deficient B cells that inhibit the production of immature B cells [65]. The signaling pathways mentioned above drastically interfere with the development of defensive humoral immunity in response to infectious pathogens in the aged population.

NK cells

Natural killer (NK) cells are innate lymphoid cells that comprise 10~15% of the circulating lymphocyte population and play an important role in early defense against pathogens and tumor cells [66]. These cytotoxic cells can be subdivided into different subsets based on the expression of the surface markers CD16 (also known as Fc-gamma receptor [FcγRIIIA]) and CD56 (also known as a neural cell adhesion molecule [N-CAM]).

The majority (about 90%) of circulating NK cells have a low-density expression of $CD56^{dim}$ that, accordingly to Lanier and coworkers, are mature NK cells with higher cytotoxic capacity [67]. On the contrary, almost 10% of NK cells that express $CD56^{bright}$ are more immature and secrete cytokines and chemokines, including IFN-γ [68,69]. With age, there is a progressive decline in the $CD56^{bright}$ population and an accumulation of the $CD56^{dim}$ population that begins to express CD57 ($CD56^{dim}CD57^{+}$ NK cells) [70]. This pool of CD56dimCD57+ cells shows high cytolytic capacity but reduced responsiveness to cytokines [71]. Moreover, impairment of NK cell cytotoxicity on a per-cell basis has also been reported [72]. Importantly, this effect has been partly attributed to the decreased expression of the NK protein 30 (NKp30), also known as natural cytotoxicity receptor 3 (NCR3 or CD337), in elderly individuals [73,74]. In centenarians, this NK subset maintains well-preserved cytotoxicity, which presumably helps this population to achieve advanced age in good conditions [75].

Neutrophils

Polymorphonuclear neutrophils (PMNs) play a pivotal role in the innate immune system representing one of the first lines of defense against pathogens. PMNs migrate from the blood to sites of inflammation and infection, where they recognize and phagocyte the invading microorganisms to kill them via different cytotoxic mechanisms, including the generation of reactive oxygen (ROS) and nitrogen (RNS) species and the

release of proteases and antimicrobial peptides [76,77]. In addition, PMNs can form neutrophil extracellular traps (NETs) that entrap and kill pathogens via oxidative and non-oxidative mechanisms [78]. Notably, in the absence of specific stimuli, their lifespan is relatively short, however, pro-inflammatory stimuli like bacterial lipopolysaccharide (LPS) can significantly raise it [79]. Even though aging, their number is preserved [80,81], some relevant age-related perturbations in neutrophil function, including dysfunctional phagocytic and chemotactic abilities, have been described [82-84]. In this regard, a reduction in free radical ROS production by neutrophils has been reported in older adults. Importantly, ROS are produced after oxidative bursts in phagosomes and are pivotally involved in the microbicidal function of these cells via induction of NET formation [85,86]. Because of these age-related effects on neutrophil function, there is a compromised ability of these cells to serve as primary responders to infections [84-88].

Monocytes and macrophages

Like neutrophils, monocytes, and macrophages are phagocytic cells critically involved in the innate response against infection. Importantly, circulating monocytes represent the precursors to tissue-resident macrophages that, upon differentiation, act as one of the leading cells deputed to host defense in response to exogenous agents [89,90]. However, several defects in monocyte and macrophage function, primarily due to cellular signaling dysregulation, have been reported with age. Importantly, in monocytes, these defects are particularly evident upon TLRs stimulation. For instance, Nyugen and coworkers [91] reported that monocytes isolated from older individuals exhibited a decreased expression of TLR1, resulting in impaired IL-6 and TNF-α production that negatively impacted the phagocytosis activity of these cells. In line with these data, Metcalf et al. [92] reported that in response to TLR4 and TLR7/8 stimulation, human monocytes from adults and old subjects showed significant differences at the transcriptional and functional levels, not observed in the absence of a stimulus. These authors demonstrated the impaired production of interferons (IFN-α and -γ), IL-1β, and chemokines like CCL20 and CCL8. Of note, the basis for part of these age-related defects in macrophages has been attributed to an altered expression of TLRs on the cell membrane of these cells with advancing age [93]. However, in their report, Boehmer and coworkers [94] observed that TLRs expression was not impacted in aging macrophages. Therefore, these authors suggested that part of the functional defects observed in macrophages, like altered cytokine production, were mainly related to intracellular signaling. Specifically, these authors reported that in response to LPS, there was impaired phosphorylation of mitogen-activated protein kinases (MAPK) like p38 and JNK. Despite these controversial results, other reports have suggested that defects at the level of TLR expression or intracellular signaling appear to be highly related to the increased susceptibility to and severity of microbial infections in the elderly population [95-98]. However, Pattabiraman et al. analyzing the responses elicited by a wide array of TLR agonists in distinct populations of murine macrophages provided data suggesting that extensive changes in TLR responsiveness are not associated with age. Of note, these authors reported that effects seen in response to TLRs stimulation could not account in full for the altered inflammatory status and cytokine production/release typical of immunosenescent macrophages. Therefore, these studies demand more investigations to elucidate the mechanisms responsible for "macrophaging" [99]. In this context, recent reports demonstrated that inflammaging could expand the content of activated M2-like macrophages that increase the inflammatory status of tissues and express several senescence markers. Therefore, this indicates that aging in macrophages impacts many processes, including TLR signaling, phagocytosis, and polarization.

INFLAMMAGING AND FRAILTY

Immunosenescence and inflammaging represent crucial contributors to age- and frailty-related ailments affecting whole systemic health [100-102].

Frailty is a complex physiological syndrome characterized by increased susceptibility to stressors and reduced physiological reserves that, from a biological point of view, is driven by a gradual and lifelong accumulation of molecular defects, including those affecting the immune system.

In this regard, several proofs have corroborated such a theory [103]. For instance, Leng et al. [104] provided the first evidence of a direct link between frailty and inflammation, showing that community-dwelling older frail individuals presented with higher serum IL-6 levels than non-frail subjects. In addition, the longitudinal InCHIANTI study showed that high levels of inflammatory molecules like IL-6, IL-1, and CRP are associated with poor overall physical performance and reduced muscle strength [105]. In line with this, the Longitudinal Aging Study of Amsterdam (LASA) identified CRP as a risk factor for frailty [101,106].

Analogously, the Women's Health and Aging Study found that IL-6 levels are higher in frail individuals than in non-frail counterparts [107]. Finally, the Newcastle 85+ study has confirmed the importance of these inflammatory markers in frailty [108].

To date, several reports demonstrated that in frail subjects, pro-inflammatory secretion appears to be driven by an altered functionality of immune cells (i.e., immunosenescence) in response to a chronic infection. Indeed, Leng and coworkers [109], showed that peripheral blood mononuclear cells (PBMC) from older frail adults, after persistent stimulation with bacterial LPS, proliferated less and augmented the release of pro-inflammatory cytokines. Further, Qu et al. [110] demonstrated that monocytes from frail older individuals exposed to LPS presented an increased expression of genes encoding cytokines and chemokines compared to non-frail counterparts. For their part, Schmaltz et al. [111] demonstrated that Cytomegalovirus (CMV) infection was associated with physical frailty and that IL-6 enhanced the extent of such association. Finally, Kawamura and colleagues [112] demonstrated that chronic exposure of mice to the LPS of Porphyromonas gingivalis (P. gingivalis), one of the major pathogenic factors for periodontitis [113,114] increased muscle atrophy participating in the development of physical frailty and sarcopenia.
Overall, the aforementioned mechanisms support the interrelation between the impairment of the functionality of immune cells (immunosenescence), the increased incidence and severity of infections observed in older subjects, and the impact on frailty [103].

AGING AND PERIODONTITIS

The oral cavity is one of the main portals of entry for several microorganisms (bacteria, viruses, and fungi) composing the human microbiome [115]. The oral microbiome, the so-called Oralome, is a fundamental component of the human microbiome and is composed of approximately 800-1000 microbial species, with oral bacteria (commensal and opportunistic) representing the main constituents [115,116]. Within the mouth, have been identified different habitats for oral microorganisms. For instance, it has been calculated that one milliliter of human saliva holds approximately 100 million bacterial cells (planktonic free-floating phase). Of note, these planktonic species represent the primary source of bacteria able to colonize the diverse soft and hard surfaces in the oral cavity. In this regard, mucosal sites (shedding surfaces) present monolayers of bacteria that regularly desquamate, like cheek and palate, or stable multilayers of biofilm-like bacteria (tongue) [113]. Alternatively, non-shedding ones, including natural and artificial teeth, orthodontic appliances, and tooth fillings, are colonized by a film of bacteria and sugars (bio-film) [114]. Different studies have demonstrated that several external factors such as diet, stress, smoke, alcohol, and food planes are associated with oral microbiome alteration, impacting the stability between commensal and pathogenic microorganisms forming the dental plaque, thus leading to oral disorders like periodontitis [117]. Importantly different bacterial "complexes" that compose this biofilm have been identified by Haffajee et al. [118] and Socransky and colleagues [119] with progression from facultative to anaerobe species finally responsible for gingivitis and periodontitis [118-120]. In this regard, these authors described three main complexes: the green/yellow complex that comprises mainly streptococci; the orange complex, with *Fusobacterium nucleatum* being the most important [121] and the red complex that includes the gram-negative periodontal pathogens *Porphyromonas (P.) gingivalis, Tannerella forsythia*, and *Treponema denticola* [113,114]. Mechanistically, the dysbiosis of periodontal pathogenic bacteria triggers a massive harmful local immune response. In addition, the augmented concentration of bacterial virulence factors, such as the LPS, stimulates the production of cytokines and inflammatory mediators (e.g., ILs, prostaglandin E2 (PGE2) and TNF-α) that contribute to alveolar bone reabsorption by osteoclasts [122]. Due to gingival tissue and bone destruction, oral pathogens and their toxic factors spread into the bloodstream (bacteremia), leading to systemic inflammation. Therefore, periodontitis represents a perfect model of inflammaging with chronic infections induced by oral pathogens dysbiosis that negatively impacts the health status of the young and old population, promoting accelerated aging. In this regard, levels of inflammatory mediators, including C-reactive protein (CRP), TNF-α, and IL-6, which are elevated in periodontitis, represent the linchpin for disorders like diabetes, cardiovascular and neurodegenerative diseases development that have been previously reviewed by us [113,123]. Moreover, it has been recently suggested that periodontal disease is a risk factor for complications of SARS-CoV-2 infection [124,125].
Importantly, a healthy immune system can prevent and tolerate the occurrence of constant acute inflammatory reactions despite a great oral microbial load. However, defects in host immunoregulation, like those observed with aging, are the major mechanism contributing to periodontitis. Indeed, several reports demonstrated the strict correlation between immunosenescence and periodontitis. For instance, Bodineau and colleagues [126] reported a substantial reduction in the ratio of gingival CD4+lymphocyte subset when comparing older with younger patients with chronic periodontitis. On the other hand, Clark et al. [127] analyzed the effects of aging on macrophages and reported that the age-related alteration in macrophages' function is responsible for the higher prevalence of this disorder and reduced recovery in old individuals compared to their younger counterparts. Along the same lines, a study from Liang

et al. [128], examining young and old macrophages under resting conditions or following infection with *P. gingivalis* demonstrated that aged macrophages presented with elevated expression of surface receptors that amplify inflammation, like the triggering receptor expressed on myeloid cells (TREM]-1) and the C5a anaphylatoxin receptor (C5aR). Interestingly, *P. gingivalis*, through direct activation of C5aR, disarms and subverts host immunity, further supporting the possibility that immunosenescence can contribute to the persistence of microbial communities that drive dysbiotic disorders and increase the susceptibility to infections [129].

THE IMPORTANCE OF ORAL HEALTH IN OLDER PERSONS

The presence of periodontitis affects human health in two ways: the spreading of bacteria into the bloodstream and inflammaging. These motivations represent an additional reason not to neglect the periodontal state of the elderly and to push national systems toward a periodontitis prevention campaign for the whole population. Indeed, among the interventions to prevent and decrease infections in older adults, emerging evidence demonstrated that the treatment of periodontitis is efficient in positively impacting general health [130].

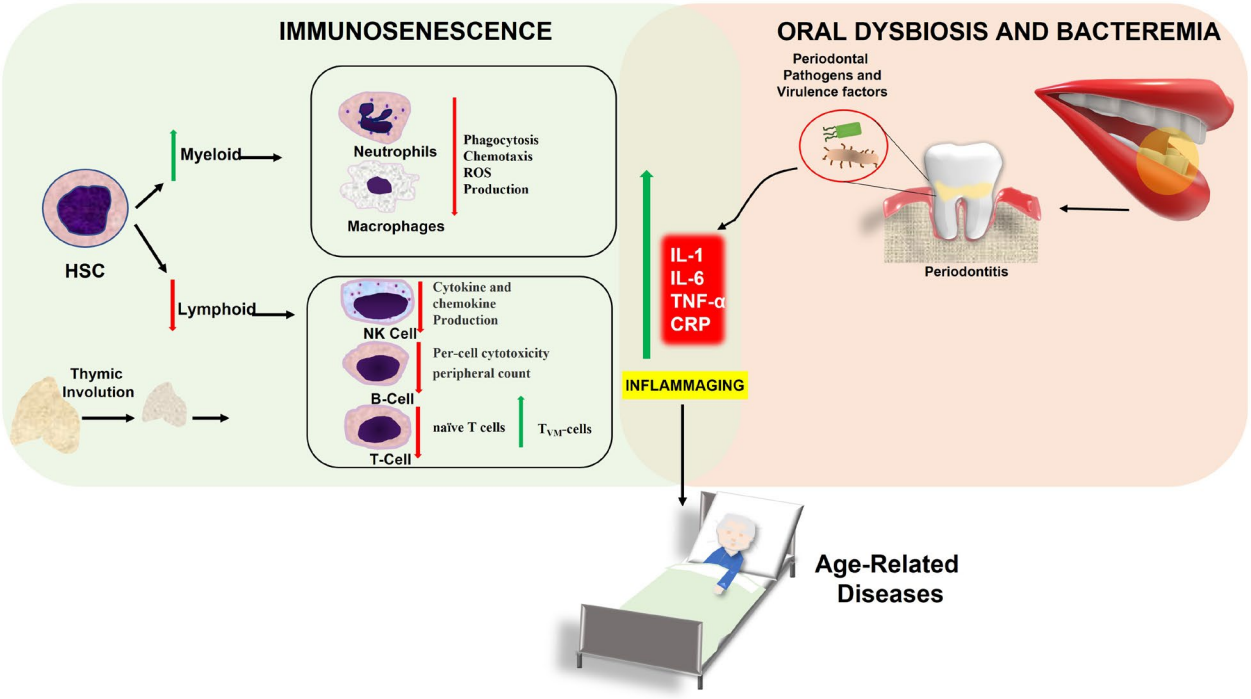
In this context, the standard treatment is to control the infection, thus preventing local inflammation. This effect can be achieved by removing the plaque by professional supra and subgingival debridement, rigorous home dental care, and correcting bone defects caused by periodontitis by employing periodontal regenerative surgery [131]. Currently, regenerative periodontal therapy is conducted by eliminating pathogens and applying biomaterials. However, recent studies support the usage of Human dental pulp stem cells (hDPSCs), one of the readily available sources of multipotent mesenchymal stem cells (MSCs), positively impacting not only the regeneration of periodontium (via a natural process) but resolving the infection and then inflammation thanks to their immunomodulatory role [131,132]. Therefore, periodontal treatment represents a valid strategy to counteract the adverse effects of the inflammaging triggered by oral dysbiosis. For instance, several studies demonstrated to positive effects of periodontal treatment on endothelial dysfunction [133-136]. This conditionoccurs during the aging process and is related to oxidative stress and vascular inflammation [137], and several pre-clinical and clinical studies have found a direct association with periodontitis. For instance, *P. gingivalis* can increase the endothelial monocyte chemoattractant protein-1 (MCP-1) expression and induce a rise in endothelin-1 levels and release [138,139]. Notably, in these studies, it has been demonstrated that periodontal treatment resulted in benefits in oral health that were accompanied with improvement in endothelial function and a reduction of circulating inflammatory markers. Beneficial effects associated with periodontal treatment were also observed in patients with type 2 diabetes [140,141] and rheumatoid arthritis [142]. Notably, these disorders, whose incidence increases with age [143,144], have been directly associated with periodontitis, also in a bidirectional manner [113,123,145] and interestingly, it has been suggested that both these disorders can develop because of premature aging (immunosenescence) of the immune system [144,146].

Further, a recent study from Schwahn and coworkers [147] reported that periodontal treatment had a favorable effect on Alzheimer's disease, the most prevalent form of dementia in the elderly, reducing brain atrophy. In this regard, we have previously reported a bidirectional link between Alzheimer's disease and periodontitis [123]. Indeed, while oral pathogens' dysbiosis and their toxic proteins represent a severe risk factor for neurodegeneration and neuroinflammation, the decline of cognitive functions in Alzheimer's disease patients negatively impacts proper oral hygiene practices, thus favoring periodontitis and tooth loss.

On the same premise, recent findings suggest that improvement in oral health contributes to the prevention of Sarcopenia, a typical syndrome of old individuals characterized by a significant loss of muscle mass and function [148]. In this regard, Han et al. [149], in a cross-sectional study, reported that periodontitis was significantly associated with Sarcopenia. In line with this study, Abe et al. [148] reported that improving oral health among community-dwelling older adults contributes to preventing Sarcopenia and Diabetes. Although experimental evidence concerning the correlation between periodontitis and Sarcopenia is limited to date, studies like the one by Kawamura et al. [112], discussed above support such relationship.

CONCLUSIVE REMARKS

This narrative Review article aimed to condense the current knowledge regarding the bidirectional association between oral health and healthy aging (Fig. 1). As discussed, immunosenescence is a major cause of augmented incidence and severity of pathogens infections, consequently leading to inflammaging in a vicious cycle that fuels itself with age. In this regard, we focused on periodontitis, a chronic inflammatory disease with high incidence in the elderly, that is characterized by a dysbiosis of pathogenic bacteria that stimulate a local and systemic inflammation representing the best example of a noxious age-related process that worsens



Abbreviations: Hematopoietic Stem Cell (HSC); Natural Killer (NK); Virtual Memory T-Cell (T_{VM}-Cell); reactive oxygen species (ROS); Interleukin (IL); Tumor Necrosis Factor alpha (TNF-α); C-Reactive protein (CRP).

Figure 1. Schematic representation summarizing the relationship between immunosenescence and periodontal disease and their effects on the development and progression of age-related disorders. As age progress, immunosenescence negatively impact on immune cells functionality and number thus augmenting the incidence and severity of oral pathogens dysbiosis and infection with consequent local and systemic inflammation thus fueling the inflammaging process. Red arrows indicate reduced.Green arrows indicate increased.

if untreated. Therefore, adequate countermeasures aiming at counteracting the adverse effects of oral dysbiosis on systemic health should be implemented at an early age in line with the idea that "prevention is better than cure". Of note, nutritional interventions, amelioration of social conditions, and correct lifestyle are undoubtedly considered optimal strategies to prevent oral disorders, given that proper oral hygiene exists. Thus, oral health status may be a predictor of longevity, and this hypothesis has been supported by recent studies showing centenarians had a lower rate of edentulism and prevalence of severe periodontal disease than their younger counterparts [150,151]. For all these reasons, several initiatives have been activated with which the Italian Society of Gerontology and Geriatrics (SIGG) should associate itself, like the one recently launched by The Gerontological Society of America called "Oral Health An Essential Element of Healthy Aging" (https://www.geron.org/programs-services/alliances-and-multi-stakeholder-collaborations/oral-health-an-essential-element-of-healthy-aging). This program has the goals of supporting older adults to keep their oral health as part of a healthy aging process and to help researchers, practitioners, educators, and policymakers to identify areas of research/activity on the subject of "oral health in older adults".

Conflict of interest statement

The authors declare no conflict of interest.

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Ethical consideration

Not applicable.

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