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1. **Review Article** [Creative Commons 4.0](https://creativecommons.org/licenses/by/4.0/)
2. Title: Periodontal disease, Cardiovascular Diseases and Aging-The cellular and molecular link

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# ABSTRACT

1. The relationship between age and the types of Non-communicable Diseases (NCDs) differed from that of Communicable Diseases. Most deaths caused by NCDs occurred in the 60–79 years age group. Similarly, periodontal disease was more prevalent in age group of 65 years and above while those below 35 years had a higher proportion of gingivitis. Cardiovascular diseases (CVD) and periodontal disease (PD) share aging as one of the risk factors. Inflammaging with increase in pro-inflammatory cytokines, cellular senescence, clonal hematopoiesis are some of the cellular and molecular pathways linking aging to CVD and PD. Therapeutic modalities that target these pathways may help mitigate the deleterious effects of aging on cardiovascular and periodontal tissues. This narrative review gives an overview of aging as the link between CVD and PD.
2. **Keywords:** Aging, Cardiovascular disease, Cellular senescence, Periodontal disease

# INTRODUCTION

1. Periodontal disease (PD) includes various chronic inflammatory conditions affecting the gums, bones, and ligaments supporting the teeth. It affects 20–50% of the global population, presenting a significant health burden.(1) Individuals with periodontitis are at an increased and accelerated risk of cardiovascular diseases (CVD), such as coronary artery disease (CAD), stroke, myocardial infarction (MI), and atherosclerosis, even when accounting for traditional risk factors like obesity and hypertension. (1)
2. Research has shown CVD prevalence of 7.2% in patients with periodontal disease; 6.6% prevalence of congestive heart disease and 25.3% prevalence of hypertension were also observed. Stroke and heart failure had prevalence of 1 and 1.1%, respectively, in presence of periodontal disease. (2)
3. PD is a polymicrobial immune-inflammatory disease caused predominently by a variety of gram-negative anaerobic bacteria. (3) Subclinical thickening of carotid intima-media has been linked to the bacterial load in the subgingival plaque beyond traditional cardiovascular risk factors.(4) The high vascularity of the oral cavity and the fragile sulcular epithelium facilitate bacterial translocation, potentially leading to bacteremia from routine activities like brushing and chewing. This bacteremia may enable bacteria to invade endothelial cells, as evidenced by their presence in atherosclerotic lesions.(5)
4. Mechanistically, bacterial biofilm formation in PD triggers an inflammatory response that spreads to deeper tissues. (6) The various pathobionts act through various mechanisms. For example, Porphyromonas gingivalis produces gingipain, an enzyme that degrades the CD14 molecule, evading immune responses and promoting inflammation through cytokines like TNFα, IL-1β, IFN-γ, and PGE2. An increase in inflammatory markers like CRP and IL-6 are linked to increased CVD risk.(6)
5. Inflammation is crucial in atherosclerosis development and chronic inflammation from periodontal bacteria and subsequent inflammatory responses, including molecular mimicry and direct vascular injury, may explain the link between periodontitis and CVD. (7)Periodontitis patients often have an atherogenic lipid profile, as well as higher oxidized LDL, which promotes atheroma development. Bacterial endotoxins and inflammatory modulators like IL-1B and TNFα affect liver and adipose metabolism, mobilizing lipoproteins into the blood to bind endotoxins and enhance their excretion.(7) Oxidative stress, significant in both acute coronary syndrome (ACS) and chronic PD, damages DNA and RNA. Several biomarkers like 8-hydroxyguanosine aswell as total antioxidant capacity, along with elevated fibrinogen and CRP levels, indicate a link between PD and ACS.(5,7)
6. PD severity correlates with a higher CAD risk, with severe PD increasing the risk by 24 to 35%. PD is also linked to aortic vascular inflammation and coronary artery calcification. PD patients have increased carotid artery intima-media thickness, unilateral carotid calcifications, and elevated CRP levels, indicating subclinical carotid disease and stroke risk.(7) Inflammation may also contribute to atrial fibrillation (AF) development. PD patients have higher systemic inflammation and an increased incidence of AF. Animal studies show that periodontitis can enhance immune activation in the atrial myocardium, disrupting electrophysiologic properties and increasing AF inducibility.(7)
7. A few of the risk factors that are shared between PD and CVD are presence of periodontal pathogens, age, stress, dietary factors. (1)Age is one of the risk determinants and cannot be modified.
8. In 1980, the proportion of the regional population aged 70 and older was 4.6%. It rose to 7.8% by 2020 and is predicted to rise to 17.4% by 2060. Across the Americas, DALY rate reductions would have decreased the number of DALYs by 18% between 2000 and 2019 but was offset by a 28% increase due to population aging and a 22% increase due to population growth. Although the region enjoyed widespread reductions in rates of disability, these improvements have not been sufficiently large to offset the pressures of population growth and population aging.(8)
9. In 2019, the burden of most NCDs in terms of the number of incident cases, deaths, prevalent cases, and DALYs was markedly lower in the < 20 years age group than that of CDs. Most deaths caused by NCDs occurred in the 60–79 years age group. Deaths caused by nervous system diseases were mainly in the > 80 years age group, while those caused by mental disorders were mainly in the 20–39 years age group.(9)
10. A knowledge of the role of Aging on the factors that predispose towards PD and CVD pathogenesis will lead to a better comprehension of the methods to control the rate of progression of the diseases in an aging population. This review gives an insight into the molecular and cellular link between CVD, periodontal disease and Aging. This in-turn will help understand the potential avenues for intervention in lowering the deleterious cardiovascular and periodontal tissue response to aging.

# Inflammaging: Cytokines in CVD

# Chronic inflammation contributes to an increase in the rate of biological aging and age-related diseases, especially CVD, type 2 diabetes, and cancer. Research shows that aging is associated with increased levels of inflammatory markers such as TNF-α, IL-1β, IL-6, and C-reactive protein CRP. This phenomenon is called as inflammaging. It acts as an indicator as well as inducer of accelerated aging. It serves as a marker of multimorbidity,premature death in older adults. Inflammaging is also linked to the immune system's reduced ability to eliminate pathogens and dysfunctional cells.(10)

## The underlying mechanisms of inflammaging involve several molecular age-related changes that lead to cellular senescence. These include impaired mitochondrial function, oxidative stress, DNA damage, inflammasome activation, and telomere shortening. However, the upregulation of proinflammatory mediators plays an important role in the development of inflammaging.(10)

## *Pro-inflammatory Cytokines and Pathways in Aging and Periodontal Inflammation*(11)

## As tissues and cells age, the levels of pro-inflammatory cytokines and their receptors increase. These elevations are also observed in inflammatory diseases, linking chronic inflammation closely with key cellular signaling pathways.

## *Interleukin-1 Family*

## IL-1, comprising IL-1β and IL-1α, is pivotal in inducing stress-induced inflammatory responses and mediating immune and inflammatory reactions. IL-1 activates immune cells and induces other pro-inflammatory cytokines like TNF-α and IL-6. It regulates cell death and survival, promoting cell death in pancreatic beta cells while enhancing neutrophil survival. Given its central role, IL-1 modulation is a target for therapeutic approaches in inflammatory diseases.(12)

## *Interleukin-6*

## IL-6 is a multifunctional cytokine vital for the acute-phase response and the pathogenesis of chronic diseases. It may act as either pro-inflammatory or anti-inflammatory depending on the context of cytokine induction. Known as the "gerontologist's cytokine" since 1993, IL-6 levels increase with age and are linked with frailty, chronic diseases, and mortality.

## *Tumor Necrosis Factor Alpha*

## TNF-α is an important regulator of inflammation, up-regulated with age. It acts beneficially as a local pro-inflammatory mediator but can be detrimental when released systemically. High TNF-α levels are associated with increased cardiovascular risk and frailty in older adults. Genetic variations in TNF-α are linked to Alzheimer's disease and myocardial infarction, suggesting that TNF-α inhibitors could be potential treatments for age-related diseases.(12)

## *Nuclear Factor-κB (NF-κB) System*

## NF-κB is a master transcription factor crucial for immune response signaling. It is sequestered in the cytoplasm by inhibitory proteins, but upon stimulation, it translocates to the nucleus and triggers pro-inflammatory gene transcription. Age-related dysregulation of NF-κB leads to increased expression of pro-inflammatory cytokines. Studies have shown enhanced activation of NF-κB in aging tissues, directly contributing to osteoclast differentiation and periodontitis.(13)

## *Inflammaging: Senescent cells*

## The proliferating as well as long-lived cells can enter a state of cell cycle arrest known as cell senescence as a result of cellular stresses, which involves significant phenotypic and functional changes. Many of these changes are driven by continuous signaling through mTOR (mechanistic target of rapamycin), which facilitates protein synthesis, increases biomass, and results in hypertrophy. Senescent cells resist apoptosis and exhibit local DNA methylation changes and global chromatin rearrangements, altering gene expression and leading to the secretion of numerous chemokines, cytokines, and tissue remodeling enzymes. This secretory profile is termed the senescence-associated secretory phenotype (SASP).(14)

## SASP evolved for the removal of senescent cells by immune cell types such as NK cells, macrophages, and T cells. Senescence plays an essential role in tissue remodeling during development, regeneration, and wound healing, and acts as a tumor suppressor. However, the failure of immunosurveillance with age, coupled with the immune evasion tactics of senescent cells through SASP, leads to their accumulation in tissues. This phenomenon is exacerbated by senescent immune cells that drive senescence in neighboring cells, as seen in a mouse model with a DNA repair factor mutation, which demonstrated accelerated aging and increased senescent cell accumulation.(14)

## Senescent cells contribute to inflammaging due to the pro-inflammatory components of the SASP, such as cytokines, chemokines, soluble receptors, metalloproteases, protease inhibitors, and growth factors. The SASP varies based on cell type and the senescence inducer, but common elements like SERPINs, GDF15, and STC1 are found in both lab-cultured senescent cells and the human plasma of aging individuals. The central signaling pathway for SASP involves NF-κB, which is crucial for SASP onset. The SASP is dynamic in nature and its composition changes over time, and it acts both autocrine and paracrine, inducing secondary senescence in neighboring cells.(14)

## Telomere dysfunction can be induced by chronic inflammation which promotes senescence, creating a feedback loop that reinforces both processes. RAGE (receptor for advanced glycation end-products) signaling mediates this reinforcement through inflammatory signaling. RAGE interacts with multiple ligands, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), promoting a pro-inflammatory cascade. RAGE expression is linked to physiological aging and sustained low-grade inflammation. The SASP component HMGB1, which binds to RAGE with high affinity, promotes inflammaging.(14)

## *Senescent cells: Periodontal disease*

## Senescent cells build up in the alveolar bone in periodontitis, contributing to deterioration of bone in an age-related manner. Periodontal ligament cells (PDLCs), include different cell types such as periodontal ligament stem cells (PDLSCs) and periodontal ligament fibroblasts.(11)

## PDLCs and PDLSCs share comparable surface marker expressions. They also have similar multipotent differentiation, and regeneration capabilities. However, with age, viability, and osteogenic differentiation of PDLCs decline. (15)This can contribute to the initiation and progression of age-related periodontal diseases.(11)

## *SASP in Periodontitis*

##  The key pro-inflammatory cytokines involved in SASP in periodontitis include IL-1α; IL-6 which is secreted by epithelial cells, lymphocytes, and macrophages when triggered by bacterial lipopolysaccharides (LPS), IL-1, and TNF-α, IL-6 promotes osteoclast formation and contributes to tissue damage; TNF-α that can enhance the expression of IL-1α, IL-6, and RANKL;(16) IFN which is involved in the immune response to periodontitis; IL-8 attracts neutrophils and other leukocytes to the site of inflammation site. IL-8 augments osteoclast differentiation, and its levels are elevated in the GCF of chronic periodontitis patients; Monocyte Chemoattractant Protein-1 (MCP-1 is secreted by cells of the immune system in response to bacterial components and inflammatory mediators. (17)

## *Cellular Senescence: Cardiovascular diseases*

## Telomeres, play an important role in maintaining chromosome stability and integrity by preventing degradation or fusion with neighboring chromosomes. Telomere shortening is strongly associated with cellular senescence, contributing to the collection of senescent cells within the vascular wall and heart, which results in deleterious alterations in structural and functional characteristics of the cardiovascular (CV) system with age.(18)

## Studies have shown that individuals with clinical or subclinical atherosclerosis often have reduced leukocyte telomere length (LTL) compared to healthy controls, even after adjusting for factors like age, sex, and race. Shorter LTL has been linked to a higher risk of ischemic and hemorrhagic strokes, as well as an increased risk of plaque formation and progression in blood vessels.(18)

## Furthermore, meta-analyses have demonstrated that individuals with the shortest LTL have a significantly higher relative risk for coronary heart disease (CHD) and cerebrovascular disease. (19,20)These findings underscore the importance of telomere length as a potential biomarker for assessing cardiovascular risk.

## Cellular senescence is also influenced by age-related defects in adrenergic signaling and calcium handling. With age, norepinephrine levels in plasma increase due to reduced clearance and increased spillover from tissues. This leads to impaired adrenergic responsiveness, characterized by decreased numbers, affinity, and internalization of beta-adrenergic receptors, particularly the beta1 subtype, and abnormalities in cyclic adenosine monophosphate (cAMP) production.(21)

## Additionally, aging affects calcium handling in cardiomyocytes. There is a reduction in calcium reuptake by the myocardial sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2a), resulting in impaired early diastolic left ventricular (LV) filling and compensatory increases in atrial contraction. Aged myocytes also exhibit decreased calcium transient amplitude and delayed propagation of calcium transients, which can contribute to mechanical inefficiency and electrophysiological abnormalities, increasing the risk of arrhythmias such as atrial fibrillation in older individuals.(21)

## *Clonal hematopoeisis*

## Clonal haematopoiesis (CH), was first linked to cardiovascular disease (CVD) in 2014 and is also known as age-related CH. A subset of CH, clonal haematopoiesis of indeterminate potential (CHIP) (22) has been associated with CVD. The clonal expansion of differentiated cells carrying the mutations that occur due to epigenetic changes from environmental factors like diet and inflammation, is linked to a 40% increased risk of CVD. (22) Notably, the risk of myocardial infarction and stroke is significantly increased. (23)In adults under 40, CHIP incidence is less than 1%, but it rises to 10% in those over 65 and 30% in those over 70. (24)In adults with a myocardial infarction history before age 50, had 2% incidence of CHIP.(25)In cardiac valve disease and heart failure, CHIP may act as disease modifier. (26)

## The potential role of CHIP in relation to CVD maybe explained on the basis of its effect on genes. CHIP mutation in the TET2 gene can leave the allele nonfunctional. In mouse models of atherosclerosis, transplanting TET2 heterozygous or null bone marrow increased atherosclerosis plaque burden in a dose-dependent manner.(27) Loss of TET2 led to increased inflammatory response in macrophages.(28) This increased inflammation likely promotes the recruitment of immune cells, driving the rise in burden of atherosclerosis.(29) In humans, mutation of TET2 gene can elevate the levels of IL-6 and TNF-alpha.(30)

## Periodontitis and CVD may be linked to aging in terms of CH as studies suggest that inflammation directs CH.(31) Research in mice indicates that inflammation enhances the selection for TET2 mutant hematopoietic stem cells. (32) Experimental systems have shown that microbial infection drives the expansion of TET2 mutant myeloid cells. These TET2 mutant cells are tolerant to death on lipopolysaccharide exposure and repopulate the bone marrow more efficiently in response to severe infection. They also proliferate more after TNF-alpha exposure. (29)If proven, this could provide a new method of the link between periodontitis and CH-associated CVD.

## *Therapeutic strategies*

## Potential therapeutic strategies to counter the aging related changes have been explored.

## *JunD and AP-1 Transcription Factors:*(33)

## JunD is a member of the AP-1 transcription factor family and it plays a crucial role in regulating cell growth, survival, and protection against oxidative stress. Reduced levels of JunD during aging contribute to endothelial dysfunction, vascular senescence, and other aging-related features.

## AP-1 as a crucial inflammatory transcription factor involved in vascular dysfunction and atherogenesis.(29) (34)Cheng et al revealed that irbesartan, an angiotensin II receptor antagonist, can downregulate AP-1 activity and suppress T-lymphocyte activation and thereby might modulate inflammation-based atherosclerotic diseases.(35) Therefore, inhibiting AP-1 could be a favourable approach to prevent the progression of atherosclerotic disease.

1. Two members of the AP-1 family, JunD and Fra1, play significant roles in regulating heart growth during hypertrophic responses. JunD, functions as an endogenous dominant negative regulator to safeguard against widespread hypertrophic growth of cardiomyocytes under pathophysiological stress.(36) Deletion of Jun has been shown to lead to progressive myocardial fibrosis, cardiomyocyte apoptosis, and changes in sarcomeric organization. (37) Components of AP-1, FosB and JunB, are capable of regulating the matrix metalloproteinase 2 (MMP-2) promoter in vivo subsequent to ischemia–reperfusion injury.(38) MMP-2, is an important component of the heart's response to injury. Restoring Jun activity in the vasculature may be a potential therapeutic strategy for combating vascular aging.

## In periodontal tissues, inhibition of AP-1 normalized the functional state of the nitric oxide cycle, reduced superoxide anion radical production and restored the activity of antioxidant enzymes, thereby protecting the periodontal tissue from oxidative damage.(39)

## Thus, optimal regulation of AP-1, may be considered for management of periodontal disease and reduce the oxidative stress related damage associated with aging.

## *Sirtuins (SIRT1):*(40)

1. Sirtuins are a family of proteins involved in regulating aging processes. SIRT1, in particular, plays a significant role in maintaining cellular homeostasis and protecting against age-related functional decline. Age-related decline in SIRT1 expression correlates with functional deficits in vascular smooth muscle cells (VSMCs), reduced stress response, and increased senescence. Activation of SIRT1 has been shown to preserve endothelial function and attenuate atherogenesis, while SIRT1 inhibition can lead to endothelial dysfunction and atherosclerosis. SIRT1 also regulates pathways involved in endothelial NO availability, inflammation, DNA damage, and oxidative stress, thus impacting arterial aging.
2. In addition, in the periodontal tissues, it has been demonstrated that inhibition of SIRT1 by sirtinol or SIRT1 siRNA inhibited the high-mobility group box 1(HMGB1)-stimulated expression of RANKL and cytokines and this suggested that inhibition of SIRT1 may weaken HMGB1-mediated periodontal bone resorption through the alteration of osteoclastogenic cytokine levels in HPLCs. (41)Thus, though the roles of the sirtuins in CVDs and periodontal disease seem conflicting, regulating the agent and identifying the optimal results will facilitate the development of modalities to alleviate the age related effects on CVD and periodontium.

## *Klotho:*(42)

Klotho is another important anti-aging protein that functions as a hormone and binds to cell-surface receptors, modulating insulin and insulin-like growth factor 1 signaling. Genetic deletion of Klotho in mice leads to aging features that occurs prematurely, while overexpression prolongs lifespan and is protective against age-associated cardiovascular and renal impairments. Incraese in plasma Klotho levels are associated with a lower risk of CVD in humans, suggesting its potential as a biomarker and therapeutic target for age-related CVD. Overall, understanding the roles of these proteins and pathways in aging and age-related CVD can potentially lead to the development of novel therapeutic interventions to improve cardiovascular health in aging populations.

## Chen et al have shown that α-klotho in serum was associated with oral health.(43)

## FGF23-α-Klotho axis helps in regulating calcium-phosphorus balance and vitamin D homeostasis. A reduction in α-Klotho levels may deteriorate the periodontal status by affecting the calcium-phosphorus balance and levels of vitamin D.(44)

## Thus Klotho may prove to be a beneficial agent for management of both CVD and PD and mitigate the effects of aging on both CVD and periodontal tissues.

# CONCLUSION

Aging, Cardiovascular disease and Periodontal disease are linked through molecular and cellular pathways. Inflammaging with associated cellular senescence, cytokine release and clonal hematopoiesis are some of the underlying linking mechanisms of the three entities. An in depth understanding of the mechanisms along with appropriate intervention strategies can help reduce the deleterious effects of aging on CVD and periodontium. Further research on the various regulators of aging, anti-cytokine agents may help in development of treatment modalities that are beneficial for abating age associated diseases of CVD and periodontium.

# DECLARATIONS

## Authors’ contributions

1. Made substantial contributions to conception, data acquisition and preparation of the manuscript: LP
2. Performed data acquisition: MK, RS, MP

## Availability of data and materials

1. Not applicable

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1. None.

## Conflicts of interest

1. All authors declared that there are no conflicts of interest

## Ethical approval and consent to participate

1. Not applicable.

## Consent for publication

1. Not applicable.

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# Supplementary Materials:

# No additional material available.