Letter to editor

Periodontal disease, Cardiovascular Diseases and Aging-The multidirectional link

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# ABSTRACT

Non-communicable diseases (NCDs) have been observed to occur more frequently in the 60–79 years age group. Similarly, periodontal disease is also more prevalent in the age group of 65 years and above. Thus, it is seen that 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 along with a change in oral microbiome. Understanding the link between CVD, PD and aging may help mitigate the deleterious effects of aging on cardiovascular and periodontal tissues.

**Keywords:** Aging, Cardiovascular disease, Cellular senescence, Periodontal disease

# INTRODUCTION

Periodontal diseases (PD) include various chronic inflammatory conditions affecting the soft and hard tissues that support the teeth and presents a significant global health burden.(1) Individuals with periodontitis are at an increased and accelerated risk of CVD with research demonstrating a CVD prevalence of 7.2% in patients with periodontal disease. (2)

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. (3) Oxidative stress, significant in both acute coronary syndrome (ACS) and chronic PD, damages DNA and RNA.(3)

Several risk factors act synergistically to increase the risk of PD and CVD. Aging is one of the risk factors that is shared between PD and CVD. (1) In 2019, most deaths caused by NCDs occurred in the 60–79 years age group.(4) Similarly periodontal disease is also more prevalent in the older age group.(5)

An insight into the relationship between CVD, periodontal disease and aging will help understand the potential avenues for intervention in lowering the deleterious effects of aging on cardiovascular and periodontal tissue response. Several factors like inflammaging, alteration in microbiome or mitochondrial dysfunction may contribute to stimulation of cells of the immune system and initiate the inflammatory process which ultimately acts as the basis of the link between CVD, PD and aging.

# *Inflammaging: cytokines in PD and 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. Inflammaging is also linked to the immune system's reduced ability to eliminate pathogens and dysfunctional cells.(6)

## This inflammatory process is also associated with periodontal disease progression.(7) The underlying mechanisms of inflammaging involve several molecular age-related changes that lead to cellular senescence. (6)

## *Cellular senescence, senescence-associated secretory phenotype (SASP), mitochondrial, immune cell and secretory cell dysfunction*

## In cellular senescence, the cells resist apoptosis and exhibit local DNA methylation 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 SASP.(8) The failure of immunosurveillance with age, coupled with the immune evasion tactics of senescent cells through SASP results in increased senescent cell accumulation. (8)

## Cellular senescence can affect cardiac function through several mechanisms, one of them being its influence of calcium handling in cardiac myocytes. This may contribute to mechanical inefficiency and electrophysiological abnormalities, increasing the risk of arrhythmias such as atrial fibrillation in older individuals.(9)

## Senescent cells build up in the alveolar bone in periodontitis, contributing to deterioration of bone in an age-related manner. In addition, with age, viability, and osteogenic differentiation of Periodontal ligament Cells decline. (10)This can contribute to the initiation and progression of age-related periodontal diseases.(7)

## Aging alters mitochondrial quality control, affecting mitochondrial shape and function. Defects in mitophagy and mitochondrial dysfunction trigger Aβ and tau accumulation, causing synaptic dysfunction. Mitochondrial dysfunction can lead to CVDs and periodontal disease by affecting oxidative stress, inflammation, apoptosis, and metabolic changes. (11)

Clark et al. (12) reported age-related variations in macrophages. It is linked to a pro-inflammatory and M1-like phenotype. In addition, there is improper polarization, diminished NO production, variations in levels of toll-like receptor expressions with a resultant decrease in regulatory action of macrophages which occurs in response to bacterial plaque and periodontal disease.(13) Aged gingival fibroblasts also demonstrate a decreased level of cell migration, proliferation and contraction, and lower α-SMA is integrated to actin stress fibers thereby affecting the healing response to tissue damage.(13)

## *Telomere shortening, RAGE signaling, PAMPs and DAMPs*

## Telomere shortening can be induced by chronic inflammation and can contribute to cellular senescence while receptor for advanced glycation end-products (RAGE) expression is linked to physiological aging and sustained low-grade inflammation. RAGE, expressed by immune cells, interact with multiple ligands, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), promoting a pro-inflammatory cascade. (8)

## Telomere shortening contributes 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.(14) In periodontitis patients, shortened telomeres in immune cells are indicative of immune system dysfunction which facilitates growth of periodontal pathogens and favour the development of oral diseases.(15)

## *Clonal hematopoeisis*

## Clonal haematopoiesis (CH) is also known as age-related CH. A subset of CH, clonal haematopoiesis of indeterminate potential (CHIP) (16) has been associated with CVD. In adults under 40 years, CHIP incidence is less than 1%, but it rises to 10% in those over 65 and 30% in those over 70. (16)

## CHIP mutation in the TET2 gene can leave the allele nonfunctional. Loss of TET2 led to increased inflammatory response in macrophages.(17) This can increase the burden of atherosclerosis.

## Periodontitis and CVD may be linked to aging in terms of CH as studies suggest that inflammation directs CH.(18) Experimental systems have shown that microbial infection drives the expansion of TET2 mutant myeloid cells which in turn causes an increase in pro-inflammatory cytokine levels.

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# *Periodontal microbiome-linking CVD, PD and aging*

P.gingivalis, a periodontal pathogen, has been demonstrated to have the property to induce platelet aggregation through hemagglutinin domain protein HgP44 which in turn furthers the atheroma formation.(19) Studies have shown that IFN-γ and IL-1β produced in response to presence of periodontal pathogen and their virulence factors are pro-atherogenic cytokines.(20) Moreover, the pro-inflammatory cytokines can subdue the anticoagulant pathways, such as the protein C pathway.(20) The cytokines can also affect the levels of Reactive Oxygen Species (ROS) thereby promoting endothelial dysfunction and development of CVD. This effect may be through an effect on endothelial Nitric Oxide Synthase(eNOS) with a resultant reduction in Nitric Oxide synthesis.(21) This can result in reduced levels of NO with resultant impaired Endothelial Function.

The concept of auto immunity mediated atherosclerosis has been postulated based on the similarity between molecular structure of anti-porphyromonas gingivalis GroEL antibodies and autologous human HSP 60. The cross-reactivity between the pathogens and the HSP 60 expressing endothelial cells may provide another explanation to the link between CVDs, strokes and periodontal pathogens. (22) Pg and Aggregatibacter actinomycetemcomitans (Aa) may penetrate into the vascular Endothelial cells(ECs) and persist in the vascular ECs with a resultant increase in the synthesis of proinflammatory mediators. (23)

Aged macrophages demonstrate lower levels of TLR4/MD-2 (24) affecting immune response to pathogen. In addition to the cellular and molecular changes due to periodontal microbiome, age related changes in the microbiome have been noted. In the age group of over 60 years, Veillonella atypica and Prevotella denticola were seen to be more. In addition, Streptococcus anginosus and Gemella sanguinis, were also increased and these are associated with CVDs, pulmonary disorders and head and neck disorders.(25)

# 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. In addition, alteration in oral microbiome can affect the CVD occurrence. An in depth understanding of the mechanisms along with appropriate intervention strategies can help reduce the deleterious effects of aging on CVD and periodontium.

**DECLARATIONS**

## Authors’ contributions

Made substantial contributions to conception, data acquisition and preparation of the manuscript: LP

Performed data acquisition: MK, RS, MP

## Availability of data and materials

Not applicable

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## Conflicts of interest

All authors declared that there are no conflicts of interest

## Ethical approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

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# Supplementary Materials:

# No additional material available