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LETTER

Periodontal disease, cardiovascular diseases and aging—the multidirectional link

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Abstract

Non-communicable diseases (NCDs) have been observed to be more prevalent in the 60–79 age group. Similarly, periodontal disease (PD) is also more prevalent in the age group of 65 years and above. Thus, cardiovascular disease (CVD) and PD appear to share aging as a common risk factor. Inflammaging with an 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 alterations in the oral microbiome. Understanding the link between CVD, PD and aging may help to 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 that affect the soft and hard tissues that support the teeth and represents a significant global health burden [1]. Individuals with periodontitis are at increased and accelerated risk of cardiovascular diseases (CVD), with research demonstrating a CVD prevalence of 7.2% in patients with PD [2].

Inflammation is crucial in atherosclerosis development and chronic inflammation by periodontal bacteria and subsequent inflammatory responses, including molecular mimicry and direct vascular injury, may explain the association between periodontitis and CVD [3]. Oxidative stress is significant in both acute coronary syndrome (ACS) and chronic PD, damaging DNA and RNA [3].

Several risk factors act synergistically to increase the risk of both PD and CVD. Aging is one of the common risk factors of PD and CVD [1]. In 2019, most deaths caused by NCDs occurred in the 60–79 age group [4]. Similarly, PD is more prevalent in the older age group [5].

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

Inflammaging: cytokines in PD and CVD

Chronic inflammation contributes to increased rates of biological aging and age-related diseases, particularly 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.

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This phenomenon is known as inflammaging. It acts as both an indicator and an inducer of accelerated aging. Inflammaging is also associated with a reduced ability of the immune system to eliminate pathogens and dysfunctional cells [6].

This inflammatory process is also associated with the progression of PD [7]. The underlying mechanisms of inflammaging involve several age-related molecular changes leading to cellular senescence [6].

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

During cellular senescence, cells resist apoptosis and exhibit local DNA methylation and global chromatin rearrangements that alter gene expression and lead to the secretion of numerous chemokines, cytokines, and tissue remodeling enzymes. This secretory profile has been termed SASP [8]. The failure of immunosurveillance with age, coupled with the immune evasion tactics of senescent cells through SASP, results in increased accumulation of senescent cells [8].

Cellular senescence can affect cardiac function through several mechanisms, one of which is its effect on calcium handling in cardiac myocytes. This can contribute to mechanical inefficiency and electrophysiological abnormalities, increasing the risk of arrhythmias such as atrial fibrillation in the elderly [9].

Senescent cells build up in the alveolar bone in periodontitis and contribute to deterioration of bone in an age-related manner. In addition, the viability and osteogenic differentiation of periodontal ligament cells decrease with age [10]. This may contribute to the initiation and progression of age-related PD [7].

Aging alters mitochondrial quality control, affecting mitochondrial shape and function. Defects in mitophagy and mitochondrial dysfunction trigger the accumulation of Aβ and tau, leading to synaptic dysfunction. Mitochondrial dysfunction can lead to CVD and PD by affecting oxidative stress, inflammation, apoptosis, and metabolic changes [11].

Clark *et al*. [12] reported age-related variations in macrophages. It is associated with a pro-inflammatory and M1-like phenotype. In addition, there is inappropriate polarization, decreased NO production, variations in the levels of Toll-like receptor expression with a resultant decrease in regulatory activity of macrophages that occurs in response to bacterial plaque and PD [13]. Aged gingival fibroblasts also show decreased levels of cell migration, proliferation, and contraction, and less α-SMA is integrated into 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 contribute to cellular senescence, while receptor for advanced glycation end products (RAGE) expression is associated with physiological aging and persistent low-grade inflammation. RAGE, expressed by immune cells, interacts with multiple ligands, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), and promotes a pro-inflammatory cascade [8].

Telomere shortening contributes to the accumulation of senescent cells in the vascular wall and heart, resulting in deleterious alterations in the structural and functional characteristics of the cardiovascular (CV) system with age [14]. In periodontitis patients, telomere shortening in immune cells indicates immune system dysfunction that facilitates the growth of periodontal pathogens and favors the development of oral disease [15].

Clonal hematopoiesis

Clonal hematopoiesis (CH) is also known as age-related CH. A subset of CH, CH of indeterminate potential (CHIP), has been associated with CVD. In adults younger than 40 years, the incidence of CHIP is less than 1%, but increases to 10% in those older than 65 years and 30% in those older than 70 years [16]. A CHIP mutation in the TET2 gene can leave the allele non-functional. Loss of TET2 leads to an increased inflammatory response in macrophages [17]. This may increase the burden of atherosclerosis.

Periodontitis and CVD may be related to aging in terms of CH, as studies suggest that inflammation controls 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.

Periodontal microbiome-linking CVD, PD and aging

Porphyromonas gingivalis (*P. gingivalis*), a periodontal pathogen, has been shown to have the ability to induce platelet aggregation through the hemagglutinin domain protein HgP44, which in turn promotes atheroma formation [19]. Studies have shown that IFN-γ and IL-1β, produced in response to the presence of periodontal pathogens and their virulence factors, are pro-atherogenic cytokines [19]. Moreover, the pro-inflammatory cytokines can suppress the anticoagulant pathways, such as the protein C pathway [20]. Cytokines may also affect the levels of reactive oxygen species (ROS), thereby promoting endothelial dysfunction and the development of CVD. This effect may be mediated by an effect on endothelial nitric oxide synthase (eNOS) with a consequent reduction in NO synthesis [21]. This may result in reduced levels of NO with consequent impaired endothelial function.

The concept of autoimmunity-mediated atherosclerosis has been postulated based on the similarity between the

molecular structure of anti-porphyromonas gingivalis GroEL antibodies and autologous human HSP 60. Cross-reactivity between pathogens and HSP 60-expressing endothelial cells may provide another explanation for the association between CVD, stroke and periodontal pathogens [22]. Pg and Aggregatibacter actinomycetemcomitans (Aa) can invade vascular endothelial cells (ECs) and persist in vascular ECs, resulting in increased synthesis of proinflammatory mediators [23].

Aged macrophages have lower levels of TLR4/MD-2, which affects the immune response to pathogens [24]. In addition to cellular and molecular changes due to the periodontal microbiome, age-related changes in the microbiome have been observed. In the age group above 60 years, *Veillonella atypica* and *Prevotella denticola* were found to be more abundant. In addition, *Streptococcus anginosus* and *Gemella sanguinis*, which are associated with CVD, pulmonary disease, and head and neck disease, were also increased [25].

Conclusions

Aging, CVD, and PD are linked by molecular and cellular pathways. Inflammation with associated cellular senescence, cytokine release, and clonal hematopoiesis are some of the underlying mechanisms linking the three entities. In addition, alterations in the oral microbiome may affect the occurrence of CVD. A thorough understanding of the mechanisms along with appropriate intervention strategies may help to reduce the deleterious effects of aging on CVD and the periodontium.

Declarations

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