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The aging process and its relation to periodontal conditions

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Abstract

Periodontal tissue destruction can cause complaints for sufferers. Inflammatory conditions of the gingiva, bleeding gums, and even tooth loss are clinical features of the destruction of the periodontal tissues. Periodontitis is an inflammatory disease involving the periodontal tissues. The prevalence of periodontium destruction increases with aging. Changes in innate and adaptive immunity that occur in the elderly also play a role in the severity of periodontitis. "Inflammaging" is a chronic inflammatory state associated with old age in humans. Periodontitis contributes to inflammaging since periodontitis in the elderly is associated with increased markers of systemic inflammation. Age-related changes also affect neutrophil function, especially antimicrobial activity, so neutrophils may become more pathological. After infiltration into the tissue, neutrophils are equipped with several antimicrobial strategies to reduce the number of antigens. Phagocytosis is the ability of neutrophils to engulf and kill microbes, but neutrophil phagocytosis is weakened in the elderly. Age-related changes affecting neutrophils, macrophages, and T cells appear to promote pathogenic immune responses and contribute to the increased prevalence of periodontal disease in aging individuals. Proper regulation of the host immune response is critical in maintaining periodontal health. This paper aims to describe the aging process and its relation to periodontal conditions.

Keywords

Periodontal, inflammation, aging, immunity, periodontitis

Introduction

Aging is a natural process that everyone must experience, thus being considered a normal and unavoidable biological phenomenon. While the aging population has continued to increase over the years, advances in medicine and public health practices in the last half of the 20th century have resulted in substantial increases in human life spans, significantly impacting the need for health services for the elderly. This is because individuals over the age of 65 years are prone to various health problems due to the aging process, therefore needing special treatment [1, 2].

The prevalence of aging-related conditions (neurodegenerative, autoimmune, inflammatory, and cardiovascular disorders, as well as increased susceptibility to infections) is increasing as a result of increasing population life expectancy [3]. With regard to dental and oral health, there is a link between oral infections and general health, such as cardiovascular disease, stroke, respiratory pneumonia, and depression, where biological evidence explains how the conditions of oral cavity influence systemic health. Thus, good oral health becomes one of the supporting factors for human health, especially in the elderly [4]. Oral health and the ability to maintain dental function throughout life have a significant impact on an individual's quality of life. Poor oral health and tooth loss have a negative impact on speech function and the ability to eat foods. In addition, it also limits people's interest in social contact [5]. In old age, maintaining dental and oral health is challenging. Even though some elderly people may have physical and/or mental situations that require special attention, dentists should not assume that all elderly people in the community have the same conditions. This presents challenges regarding the design and implementation of comprehensive preventive dentistry protocols for the elderly. In order to meet patient needs, specific protocols must be adapted. However, there are several factors common to the elderly that may influence the design and implementation of these protocols [2].

One of the diseases of the oral cavity that mostly occurs in the elderly is periodontitis or inflammation of the periodontium (tissue supporting the teeth). Since periodontal health and chronic disease can be directly related to aging, more attention should be paid to the fact that periodontal health problems such as periodontitis that bring discomfort may occur. Periodontitis is a disease that occurs due to a complex interaction between the host and the subgingival microbiota, leading to periodontal tissue destruction [6]. Further damage from periodontitis can lead to tooth loss. The primary etiology of bacterial infection in periodontitis has been demonstrated in previous studies. In addition, the host's immune response has also been proven to play a role in the occurrence of destruction in patients with periodontitis, especially in the elderly such as gingival recession and tooth mobility [7, 8]. In addition to the above factors, there are a number of other factors contributing to the development of periodontal disease. Information about changes in the periodontal tissue in the elderly will be discussed in this paper.

Changes in immunity in the elderly

The aging process in humans impacts various systems, particularly the immune system, causing sensitization and changes in immune activation, along with inflammatory processes. This eventually leads to increased susceptibility to infection, increased neoplastic events, and increased frequency of autoimmune diseases with age [9]. To describe age-related changes in the immune response that result in chronic and elevated inflammations and partially contribute to the increased prevalence of inflammatory diseases in the elderly, the term "inflammaging" is widely used [10].

Pathological changes that occur in general contribute to the occurrence of inflammaging or immunosenescence. Inflammaging is an increase and dysregulation of the inflammatory response that occurs with age and often associated with a chronic inflammatory component that underlies numerous age-related diseases. Meanwhile, immunosenescence is an age-related dysregulation of the immune response that leads to an immunocompromised state and contributes to increased susceptibility to diseases [11]. Even in healthy older people, there are increased levels of circulating pro-inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) compared with young adults. Inflammaging is associated with a chronic inflammatory component that underlies many age-related diseases [12, 13]. Franceschi et al. [14] proposed the need for a "network theory of aging" which emphasizes the broad impact of aging on the host's response systems in responding to and effectively managing multiple deleterious challenges to the host, regardless of the intrinsic inflammaging environment that occurs. The link between aging and inflammatory disease is a highly convoluted process with no clear causality or directionality. Therefore, further analysis of the inflammatory process and the role of immune factors in the aging process as well as its relation to periodontal conditions poses its own challenges [4–15].

The role of innate immune cells in periodontal conditions in elderly

The size of most innate immune cells remains stable or slightly decreases with age. However, numerous aspects of the effector function of innate immune cells decline along with the aging process, including the functions of neutrophils, macrophages, dendritic cells (DCs), and natural killer cells, which are the main innate immune cells that enter the immune system. This also influences the inflammatory environment conditions of the periodontal tissues during the course of the disease [16–18]. In the elderly, neutrophil chemotaxis is significantly impaired, including the processes of migration and release of neutrophils to and from sites of inflammation, thus affecting the initiation and resolution of inflammaging. In addition, neutrophils of older individuals also show impaired phagocytosis, reduced capacity to kill phagocytosed microorganisms, and decreased NETosis [neutrophil extracellular traps (NETs) are released during a form of pathogen-induced cell death] [16–18]. Healthy and diseased conditions are characterized in part by differences in the number of locally present neutrophils. Therefore, it is important to understand if age affects the number of neutrophils in the tissue [19]. As the healthy and diseased states of an individual are partially characterized by differences in the number of neutrophils present locally, it is absolutely essential to understand that age may affect the number of neutrophils in the tissue [19]. The ability of neutrophils to respond to chemoattractants and to migrate to sites of inflammation appears to either persist with age or show a slight reduction in the response. The number of neutrophils capable of responding to infection also remains largely the same in an aging population [20, 21].

Neutrophils

As mentioned previously, the total number of circulating neutrophil cells does not change in old age. In addition, neutrophils in both young and old individuals display comparable molecular expression and capacity for adhesion to endothelial cells. On the other hand, the neutrophil chemotaxis that occurs in response to *in vitro* stimulation with granulocyte-macrophage colony-stimulating factor (GM-CSF) or *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) is significantly reduced in old age, even in healthy elderly people [18, 22]. In the elderly, neutrophils also show increased activity of cytokine signaling inhibitory molecules, such as Src-homology region 2 (SH2) domain-containing phosphatase-1 (SHP-1) and suppressors of cytokine signaling (SOCS), which explains the decreased potency of GM-CSF and the activation of oxidative burst in the neutrophils [23]. As an antimicrobial defense mechanism, neutrophils can also produce reactive oxygen species (ROS). They release intracellular ROS to kill phagocytosed microbes or extracellularly kill microbes in tissues. In the elderly, increased production of ROS is associated with increased levels of circulating pro-inflammatory cytokines [24]. Phagocytosis of apoptotic cells is impaired in old age, i.e., damage combined with apoptotic neutrophils, which is accelerated during infection or inflammation, contributes to inflammatory tissue damage due to necrosis of unclean apoptotic neutrophils and release of toxic substances [4].

To maintain periodontal health, tight regulation of the host's inflammatory response to the oral microbes that inhabit these tissues is highly necessary. This is because its ability to elicit an effective and sufficient immune response to treat invasive oral pathogens may be decreased as a result of immunosenescence. Likewise, inflammaging can cause a hyper-reaction to inflammatory stimuli, causing collateral damage to the periodontal tissues [10]. In both healthy and diseased states of an individual, neutrophils are present in the periodontium. Chemotactic signaling cascades from oral microorganisms stimulate local recruitment of neutrophils to the periodontium. At sites of inflammation, neutrophils emerge from the small blood vessels, enter the gingival tissue, and continue their migration to the gingival sulcus, where there are numerous microorganisms and their associated chemoattractants [25]. Even in healthy clinical conditions, neutrophils are also found in healthy tissue due to stimulation by oral microorganisms that are persistent in the gingival sulcus. A significant increase in the number of neutrophils in the periodontium and gingival sulcus marks the onset of periodontal disease, in which there is a substantial increase in endogenous chemoattractant signals, i.e., pro-inflammatory signals from the epithelium, and exogenous signals, i.e., lipopolysaccharides (LPSs) from local bacterial plaques that cause local influx of neutrophils [25–27].

The explanation above emphasizes that the aging process affects one's immune and inflammatory responses, where changes that occur with age may increase one's susceptibility to chronic diseases such as periodontitis [28]. The age-related decrease in phagocytosis and microbicidal activity in neutrophils and macrophages may lead to uncontrolled growth of periodontal bacteria into the dysbiotic community. Meanwhile, the age-related increase in prostaglandin E_2 (PGE_2) production by macrophages may result in bone loss, and the age-related increase in the number of DCs in the periodontium as well as their basal nuclear factor kappa B (NF-κB) activity may cause increased local inflammation [28, 29]. In patients with periodontitis, the peripheral blood neutrophils exhibit a hyper-responsive phenotype in terms of production of ROS, even in the absence of exogenous stimuli. On this account, neutrophils recruited to the periodontium may contribute to periodontal pathogenesis, at least in part, by causing damage to oxidative tissues [30, 31].

Macrophages

The innate immune dysfunction in the elderly may be caused by inefficient communication between macrophages (or other innate immune cells) and tissues, expressing lower levels of adhesion molecules and showing reduced responses to growth factors. Generally, there are two types of macrophages, namely: tissue-dwelling macrophages and circulating monocyte-derived macrophages. Circulating monocyte-derived macrophages appear in tissues in response to infection or injury, where circulating monocytes are attracted locally, differentiate into macrophages, and migrate into the tissues [32, 33].

The functions of macrophages include engulfing and degrading apoptotic cells, cellular debris, and damaged tissues after infection and injury, or as part of normal homeostatic functions in the tissues. A repertoire of toll-like receptors and pattern-recognition receptors in macrophages detects necrotic and injured tissues or foreign LPSs from invasive microbes so as to detect and respond appropriately [34]. With regard to periodontitis, macrophages specifically respond to periodontal pathogens. When stimulated with *Porphyromonas gingivalis* and *Aggregatibacter* (*A.*) *actinomycetemcomitans*, macrophages show an increased inflammatory response by producing pro-inflammatory cytokines. Macrophages can mount a unique response to individual pathogens, whereby *A. actinomycetemcomitans* stimulates increased expression of chemokines that promotes recruitment of T-cells. During an increased microbial infection, macrophages enhance the immune response by releasing pro-inflammatory cytokines that promote the further recruitment of immune cells [35].

Along with the aging process, there is a decrease in several functions of monocytes or macrophages, including chemotaxis, phagocytosis, production of certain cytokines/chemokines, ROS or reactive nitrogen species (RNS), and expression of major histocompatibility complex (MHC) class II and costimulatory molecules. Conversely, the production of PGE_2 by activated macrophages of the elderly increases, compared to younger subjects. This explains the inhibition of MHC class II expression and IL-12 production in the elderly [32, 36, 37].

Dendritic cells

In the elderly, there is a decline in several functions of myeloid DCs (mDCs), including chemotaxis, endocytosis, IL-12 production, and antigen-presenting cells, which then result in suppression of naive T cells activation [36, 37]. Concomitant with the aging process, plasmacytoid DCs (pDCs), which are vital for host defense against viruses, show reduced production of type I and type III interferons, partly due to impaired phosphorylation of an important transcription factor (*IRF-7*). The predominant condition of DCs in elderly subjects may contribute to an increased reactivity of these cells to antigens such as DNA, which in turn may lead to age-related autoimmune inflammation [38, 39], impairments in the migration and function of macrophages and DCs. In addition, changes in DC maturation and cross-linking with T cells have also been proven to contribute to the loss of antigenic tolerance in the elderly [40, 41]. With this regard, aging appears to increase the gingival anaerobic environment, coupled with a marked decrease in the ability of gingival tissues/cells to sense and respond to microbes, particularly invasive pathogens [42]. Various

factors contribute to age-related immune dysregulation. In addition to the innate immune system, adaptive immune cells are also involved in the pathogenesis of periodontal disease in an aging population [43].

The role of adaptive immune cells in periodontal conditions in the elderly

The adaptive immune system, whose specificity stems from the diversity of antigen receptors, is largely determined by cellular interactions that involve specific antigen receptors, cellular activation, and molecular effector functions of cells and biomolecules. This system has two main features, namely: (1) diverse antigen-recognition capacity by lymphocyte populations (naive lymphocytes); and (2) antigen-recognizing and long-lived lymphocytes (memory lymphocytes). If the innate immune system is unable to remove antigenic stimuli or stressors, it will induce and recruit cells of the adaptive immune response [9, 42]. Two major changes responsible for immune sensitization are decreased overall antigen-specific immunity due to loss of numbers of naive and regulatory T lymphocytes and decreased formation of progenitor B cells in the bone marrow [44].

T cells are important drivers of the adaptive immune response which display a heterogeneous repertoire that can recognize a variety of antigens. Helper T cells are the most abundant subpopulation of T cells found in the gingiva. These cells are generally characterized as T-helper 1 (Th1) or Th2 subsets. Th1 subset is a pro-inflammatory phenotype which produces various cytokines and chemokines that can inhibit the osteolytic process in periodontal disease [45]. Meanwhile, Th2 cells fight inflammation by secreting anti-inflammatory cytokine profiles and activating B cells. In the periodontium, Th2 cells activate and promote the expansion of B cell subsets that produce antibodies against oral pathogens [46]. Cytotoxic CD8+ T lymphocytes are also found in healthy gingiva and increase in number in the incidence of periodontal disease. However, their pathogenic contribution to periodontal disease is not fully understood [47]. Adaptive immune cells decline with age due to various factors, including decreased production of naive T cells, decreased diversity of antigen-recognition repertoires, impairments in signal transduction in T cells with altered induction cytokine patterns, and reduced clonal expansion and antigen-specific function of T and B cells [48]. Such decreased production of naive T cells is partially related to the involution of the thymus, which is the site for naive T cells' production. A decrease in the number of naive T cells causes a reduced antigen-specific immunity, thus increasing the susceptibility to infections. Age-related changes also affect T-cell antigen receptors and may further limit T-cell expansion and differentiation. In addition, the frequency of lymphoid progenitor B cells continues to decline along with the aging process, as hematopoietic stem cells undergo myeloid skewing commitment at the expense of lymphoid progenitors [49].

The aging population has demonstrated changes in both innate and adaptive immunity cells, and the term "immunosenescence" has been used to refer to a decrease in the immune response [50]. This ultimately leads to an unwanted increase in inflammation and contributes to aging, a degenerative process with mitochondrial and cell damages due to oxidative stress that is influenced by genetic and environmental factors, affecting normal cellular functions. The combination of these altered responses distorts immunocompetence, enabling the incidences of various age-related diseases such as autoimmunity and cancer, and increasing susceptibility to various infections, including periodontitis. Until today, various health problems in the elderly remain major concern in all fields of medicine and dentistry [10, 51, 52].

Periodontal changes in the elderly

There is an increased susceptibility to several autoimmune, infectious, and inflammatory diseases in aging individuals. This includes periodontitis, which is characterized by physiological loss of the periodontal attachment and alveolar bone [42]. Numerous immune and non-immune cells in the periodontium communicate with osteoblasts and osteoclasts which modulate the physiological balance of bone formation and resorption. Cytokines generated by the host's innate and adaptive immune responses also interfere with local bone homeostasis and osteoclastogenesis. Age-induced changes in the functions of both innate

and adaptive immune cells are suspected to have an impact on bone metabolism and remodeling, which are directly involved in periodontal disease [53].

Periodontal disease is a complex disease with various potential contributing factors, which include genetic and epigenetic influences, patient behavior, the administration of certain medication, and environmental factors, promoting the initiation and development of the disease [54]. In addition, the periodontal inflammatory response is also modulated by several factors, i.e., genetic background, immuno-inflammatory status, presence of environmental stressors, and incidence of systemic diseases [55]. In aging individuals, increased inflammation in the periodontium results in weaken immunity, leading to persistence of chronic pathogens and continuous destructive inflammation with the help of immunity. Numerous systemic health conditions are associated with translocation of bacteria through the damaged periodontal tissues, causing a chronic increase in the systemic inflammatory response. Furthermore, other risk factors for common disease processes predispose these conditions [56, 57]. Aging can affect periodontal inflammation, making the elderly more susceptible to periodontitis. The increasing prevalence and severity of periodontitis in the elderly reflects the cumulative effects of prolonged exposure to periodontal microbial challenges [8]. In this regard, the aging process creates an environment that allows for a greater prevalence of periodontitis, chronic infections, and persistent local and systemic inflammations, thereby encouraging the development of unhealthy aging [58].

From a clinical point of view, an initial review of patient factors other than routine clinical measures, such as probing pocket depth, can yield many insights that will greatly aid in treatment [6, 59]. During the aging process, the functions of the cells in the periodontal tissues also experience changes. Age-related loss of collagen in connective tissue turnover may manifest as increased deregulation of collagen phagocytosis, where the loss of collagen occurs due to the degradation of collagen beyond its new synthesis [60]. Aging subjects are more susceptible to periodontal infection and their condition becomes more severe. Less functional innate and adaptive immune responses, coupled with slower cell metabolism and healing capacities, can increase the risk of periodontal disease. Thus, it is predictable that in elderly patients with periodontitis, immune factors and periodontal biologic conditions will be more challenging during treatment than in younger subjects [6].

For those over the age of 50, periodontal attachment loss increases dramatically with age and can also result in tooth loss in some individuals [6]. In the elderly, gingival recession occurs in a different pattern. This suggests that periodontal conditions do not necessarily present with deep pocket depths, but show evidence of gingival recession and loss of alveolar bone instead [61]. Along with the aging process, there is a decrease in fibroblasts and a more organized structure in the periodontal ligament, concomitant with changes in the gingival connective tissue. In addition, there is an increase in the width of the cementum, which is more significant in the apical and lingual areas [62, 63].

Age, number of remaining teeth, and cultural background are major variables that affect quality of life related to dental and oral health. One of the most essential ways to improve it is to prevent tooth loss at an older age [64]. Efforts should be dedicated to improving oral self-perception in the elderly; this also includes the provision of oral health information, self-efficacy support, and health risk education which are important factors in increasing the chance of successful therapy in all patients. Furthermore, public health policy should focus on preventing all significant risk factors, by using lifestyle approaches from an early age to reduce the risk of further disease [65].

Conclusions

Efforts to increase people's life expectancy become a challenge for health practitioners in providing treatments, especially in oral care which includes the treatment of periodontal disease. This is especially challenging for the elderly, among whom various periodontal changes occur due to innate and adaptive immune factors. As it is difficult to maintain healthy periodontal conditions for the elderly, early preventions are extremely necessary to be done from a young age so that severe periodontal tissue destruction does not occur later in life.

Abbreviations

DCs: dendritic cells

IL-6: interleukin-6

ROS: reactive oxygen species

Th1: T-helper 1

Declarations

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Author contributions

PW: Conceptualization, Writing—original draft, Writing—review & editing.

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The author declares that there are no conflicts of interest.

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