Highlight the Effect of Pro-inflammatory Mediators in the pathogenesis of Periodontal Diseases and Alzheimer's Disease

Nada Hashim[1], Rasha Babiker [1], Muhammed Rahman [1], Riham Mohammed [1], and Krishna Nallan[1]

[1]RAK Medical and Health Sciences University

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Abstract

Alzheimer's disease (AD) is a neurological condition that is significantly more prevalent when people become older. It may start out early or late. A rise in levels of proinflammatory cytokines and microglial activation, both of which contribute to the central nervous system's inflammatory state, are characteristics of AD (CNS). As opposed to this, periodontitis is a widespread oral infection brought on by gram-negative anaerobic bacteria. By releasing proinflammatory cytokines into the systemic circulation, periodontitis can be classified as a "low-grade systemic disease." Periodontitis and AD are linked by inflammation, which is recognized to play a crucial influence in both the illness and treatment process. The current review sought to highlight the effects of pro-inflammatory cytokines, which are released during periodontal and Alzheimer's diseases in the pathophysiology of both conditions. It also addresses the puzzling relationship between AD and periodontitis, highlighting the etiology, and potential ramifications.

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Nada Hashim, Assistant Professor of Periodontology, RAK College of Dental Sciences, RAK Medical & Health Sciences University, Ras al-Khaimah, UAE.

Corresponding author. Email: nada.tawfig@mhsu.ac.ae

Rasha Babiker: Assistant Professor of Physiology, RAK College of Medical Sciences, RAK Medical & Health Sciences University, Ras-al-Khaimah, UAE.

Email:*rashababiker@rakmhsu.ac.ae*

Mohammed Mustahsen Rehman: Professor of Periodontology, RAK College of Dental Sciences, RAK Medical & Health Sciences University, Ras al-Khaimah, UAE.

Email:*mustahsen@rakmhsu.ac.ae*

Riham Mohammed: Assistant Professor of Oral and Maxillofacial Surgery, RAK College of Dental Sciences, RAK Medical & Health Sciences University, Ras al-Khaimah, UAE.

Email: riham.abdelraouf@rakmhsu.ac.ae**Krishna Chytanya Nallan** : Assistant Professor of Oral Radiology, RAK College of Dental Sciences, RAK Medical & Health Sciences University, Ras al-Khaimah, UAE.

Email: krishna.chytanya@rakmhsu.ac.ae

Abstract

Alzheimer's disease (AD) is a neurological condition that is significantly more prevalent when people become older. It may start out early or late. A rise in levels of proinflammatory cytokines and microglial activation, both of which contribute to the central nervous system's inflammatory state, are characteristics of AD (CNS). As opposed to this, periodontitis is a widespread oral infection brought on by gram-negative anaerobic bacteria. By releasing proinflammatory cytokines into the systemic circulation, periodontitis can be classified as a "low-grade systemic disease." Periodontitis and AD are linked by inflammation, which is recognized to play a crucial influence in both the illness and treatment process.

The current review sought to highlight the effects of pro-inflammatory cytokines, which are released during periodontal and Alzheimer's diseases in the pathophysiology of both conditions. It also addresses the puzzling relationship between AD and periodontitis, highlighting the etiology, and potential ramifications.

Keywords

Alzheimer's disease, periodontal disease, pro-inflammatory cytokines, TNFα, IL-1, resolution of inflammation

Background

Alzheimer's disease (AD) is a fatal brain condition that predominantly affects older people and is a major global health concern for people in their senior years. Alzheimer's disease prevalence increases sharply with aging, reaching about 50% in persons over the age of 85 (1).

Periodontitis is more common in elderly people due to its chronic and cumulative nature, with two-thirds (68%) of those over the age of 65 suffering from chronic periodontitis. Also, individuals aged 70 to 81 years old had a considerably greater frequency of periodontitis than those aged 50 to 59 years old (2,3). Worldwide, around 11% of people suffer from severe periodontitis (4).

Unless an important medical improvement, the incidence of AD will probably double by the middle of this century, finally leading to a worldwide incidence of roughly 131.5 million (5,6). Great deals of fresh cases of AD are random and late-onset illnesses.

In the next 50 years, it's predicted that AD and periodontal disease would impact about 14 million individuals (1,7) as the population at large ages and their lifespan rises. Switching to newer treatment techniques that can be efficient towards possible contributing factors for both conditions can help lower the incidence of AD and periodontal diseases (1).

Both AD and periodontitis may contain an early or late start. Early-onset AD and periodontitis are assumed to be inheritable, whereas late-onset AD and periodontal disease, which effects a lot of people, appears to be the result of an interplay of genetic and extrinsic factors. Age, type 2 diabetes, and teaching are all connected with risk for both disorders. In addition, periodontitis is regarded as being one of the potential risk variables for AD (1,7).

The "chicken or egg first" argument may be made from a significant portion of cross-sectional and longitudinal correlation studies. Is the association between AD and periodontal disease entirely due to Alzheimer's Disease patients' failure to sufficiently eliminate a dysbiotic biofilm using a regular plaque control program? Or, can the infiltration of inflammation-causing cytokines into the cerebral cortex as a result of the host's contact with pathogenic microbiota have a function in the commencement and progression of AD? (8,9)

There is emerging confirmation that periodontitis can damage all parts of the body and is an independent risk factor for AD. Hence, here may be a link between the mediators of inflammation generated by the contact of oral infections with the host's cells and AD. This would be especially noteworthy given the age-related frequency of chronic periodontitis and AD (10).

The continual growth in an internal pro-inflammatory status with age maintains the level of susceptibility to periodontitis and AD (11).

Inflammatory mediators in the pathogenesis of AD

There is mounting proof that connections between glial cells and neurons controlled by cytokines in the CNS, which regulate inflammation, cause cognitive impairment. Furthermore, it has been shown that AD is linked to an increase in pro-inflammatory cytokines, this may contribute to the creation of plaque and speed up the degeneration of nerve cells (12).

Several of these mediators, such as "interleukin (IL)-6, TNFα, and IFN- "rise during the prodromal stage of AD. These cytokines are elevated when AD first starts to develop. These results, therefore, confirm the significance of these cytokines in the development of chronic inflammation in AD. Several cytokines, including "IL-1, -6, -10, -12, and -18, IFN-, and TNFα" have been proposed as AD biomarkers as a result of these observations (13).

When microglial cells are stimulated, they release proinflammatory cytokines such as tumor necrosis factor (TNFα), interleukin (IL)-1, and IL-6. These enhanced proinflammatory cytokines may then drive glial cells to release more amyloid β-peptide (AβP), P-Tau, and proinflammatory molecules via paracrine and/or

autocrine mechanisms. As a consequence, mediators of inflammation play a dual effect in neurodegeneration by activating glial cells while simultaneously activating molecular pathways. "TNF-, IL-1, and IL-6" can increase the manufacture of AβP and the phosphorylation of tau protein, while AβPand P-Tau may increase glial cell production of "TNFα, IL-1, and IL-6" (1,14).

In AD, inflammation has developed a distinct system through which cytokines, such as TNF-, IL-6, and IL-1, may affect and connect the blood-brain barrier (BBB), leading to this to discharge proinflammatory cytokines which render it easier to penetrate to cells, permitting the flow of leukocytes that to the cerebral and triggering off a series of occurrences within the mind that result in additional production of the proinflammatory mediators by microglia and astrocytes (15).

It is commonly accepted that a key element in leukocyte recruitment to the Brain and neuroinflammation is the rise of "IL-1, IL-6, and TNFα". Astrocytic and microglial activation, as well as the encouragement of A deposition in the brain, are features of this reaction. Moreover, inducible "nitric oxide (NO) synthase (NOS) synthesis" and activity in the brain as well as NO metabolite overflow into the CSF fluid are highly promoted by "IL-1 and TNFα"(16).

Recently, it was discovered that persons with severe forms of AD have greater TNF- levels when their NO levels are high. In addition, genetic and epidemiological research has linked greater TNFα levels in the brain to an increased risk of Alzheimer's disease (17).

TNFα may enhance the accumulation of tau proteins in neurites via generating ROS. Another study demonstrated that a considerable decline in TNFα and IL-6 levels linked with cognition and behavioural improvement in a transgenic mouse model of AD (18).

Owing to the essential role that inflammatory performs in the progression of AD, a variety of inflammatory mediators, notably TNFα, IL-1α, and IL-1B, are being proposed as AD indicators. In addition, periodontitis and other disorders connected to localized or generalized inflammation have been indicated as risk factors for the formation of AD.

For example, higher systemic "IL-6 and C-reactive protein (CRP)" levels have been related to lower cognitive performance and a higher risk of AD (19).

More recently, it was shown that IL-1 was the factor most substantially linked to the progression of moderate cognitive impairment to dementia when several cytokines were examined in the blood of people on the AD spectrum (20).

TNFα has also been connected to memory problems in a similar manner. An acute systemic inflammatory event and high baseline plasma TNFα levels were shown to be associated with a tenfold higher incidence of cognitive impairment over a half-year period in one longitudinal research. Moreover, peripheral injection of a TNFαtargeting receptor prevented memory loss brought on by amyloid (21,22).

Inflammatory Mediators in periodontal disease

Inflammatory mediators, which are generated by immune and inflammatory cells in reaction to the accumulation of biofilm on the teeth, have a role in both the beginning and progression of periodontal disease. It has become obvious that the bulk of tissue destruction in the periodontium is caused by host-derived enzymes and mediators including cytokines and other inflammatory mediators like PGE2. Paradoxically, tissue breakdown is also a function of the host systems that protect against certain diseases. Therefore, the spatial course of the inflammation that spreads to the cartilage and periodontal ligaments is an essential variable which could determine whether the damaging impact is predominant over infection administration, and the contribution of pro-inflammatory mediators in the inflammatory process is crucial (23).

Cytokines are crucial in a myriad of physiological tasks, but when cytokines circulation improperly, they may induce disease. The ratio of pro- and anti-inflammation in periodontal conditions is tilted towards proinflammatory activity. "Interleukin-1 (IL-1) and IL-6", as well as the tumor necrosis factor (TNFα), appears to have critical functions in periodontal tissue degeneration (24,25).

The host is composed of tissue cells (neutrophils and monocytes) expressing IL-1 and -1, IL-6, TNFα, and prostanoids; ultimately opening the route for further destruction of periodontal tissues. Hence, the host reaction has a dual role that motivates tissue enzymes known as proteolytic enzymes to produce them overly, ultimately driving the host to self-destruct (26).

How inflammatory mediators produced in periodontitis can be a risk for developing AD

The host response is crucial in eliciting systemic consequences in periodontal infection because it releases an array of inflammatory mediators, including cytokines, to combat periodontal bacteria that penetrate the systemic circulation.Periodontal infections and their products trigger an inflammatory response in the Brain. It is well known and validated by evidence that the presence of inflammation in the Brain causes cognitive impairment, including that exhibited in AD. This inflammatory dysfunction is induced by cytokine-mediated interactions between neurons and glial cells (27, 28).

Periodontitis may lead to the development of AD as a consequence of the host's response to periodontal infections, which produces a rise in the production of proinflammatory cytokines. This triggers a cascade of cytokine and pro-inflammatory substances to be produced into the circulatory system, leading in a systemic inflammation load and an episode of systemically/peripheral inflammation. These pro-inflammatory chemicals have a propensity to permeate the BBB and reach brain regions. These results in the priming/activation of cells called microglial cells and the deleterious implications of neuronal injury. "TNFα, TGF-, and chemokines (monocyte chemotactic protein, IL-8, macrophage migration inhibitory variable, and monokine generated by -interferon)" were additionally reported as serum and plasma indicators for the cause of AD (29).

The synthesis of cytokines, particularly TNFα, during inflammation plays a crucial influence in neurodegenerative disorders. Gliosis, demyelination, BBB degradation, and cell death are triggered by TNFα's amplification of the inflammatory process. In light of this, TNFα is critical to the neurodegenerative process (28).

Resolution of inflammation IN AD and periodontal disease

The ultimate goal of an inflammatory reaction is its prompt cessation in order to prevent it from becoming chronic and having possible negative repercussions. In reality, continuous inflammation is the source of a variety of chronic disorders, such AD and periodontal (30).

A lot of active and well-coordinated measures must be implemented for that inflammation to be effectively treated. They include the end of neutrophil employment, the clearance of apoptotic neutrophil by mucosal phagocytes that (efferocytosis), the commencement of tissue repair, and the elevation of regulating or pro-resolution factors in contrast to an elevation of proinflammatory factors (31).

During the resolving phase of inflammation, a 'lipid-mediator class shift' occurs. This temporal shift represents a shift from a pro-inflammatory milieu rich in prostaglandins and leukotrienes to one rich in pro-resolving mediators such as "arachidonic acid-derived lipoxins and omega-3 polyunsaturated fatty acid-derived resolvins and protectins". "Docosahexaenoic acid (D series resolvins) or eicosapentaenoic acid are the sources of resolvins (E series resolvins)". Lipoxins and resolvins, when released into the arterial lumen, can limit neutrophil transmigration to tissues via a variety of processes, including regulation of sticky molecules in both neutrophils and the endothelium. Moreover, "lipoxins and resolvin"s can limit neutrophil recruitment by decreasing the expression of 2 integrins and ICAM-1 and increasing endothelial cell production of nitric oxide, which is an inhibitor of leukocyte adherence to vascular endothelium (31-33).

The resolve of inflammation is not merely an indifferent cessation of inflammation; instead, it constitutes an active biochemical and metabolic procedure that is controlled by particular pro-resolving lipids mediators. Lipoxins, resolvins, and protectins belong to pro-resolving lipids intermediaries. It is commonly known that particular pro-resolving lipid mediators are essential to minimize inflammation-related damage to tissues. Receptor agonists act as pro-resolving lipid mediators. These actively suggest the cessation of inflammation by attaching to receptors that are only engaged throughout inflammation: feedback signalling as compared

to nonspecific inhibitory. The research indicates that the exogenous injection of particular pro-resolving mediators of lipids activates their receptors and inhibits chronic inflammation in circumstances of failure of resolution (34-36).

The most exciting pro-resolution mediation at now are a spectrum of mediators made up of lipids derived from "polyunsaturated fatty acids (PUFAs). These include maresin, resolvin-D, resolvin-E, protectin, and lipoxin (LX)".

Arachidonic acid, an omega-6 polyunsaturated fatty acid, is the source of lipoxins. LXs are created fast and work either in a paracrine or autocrine method. "Formylpeptide receptor2/lipoxin A4 receptor (ALX/FPR2)", a member of the formyl peptide receptor superfamily, is the binding site for lipoxinA4 (LXA4). The power of LXs to inhibit the attraction of neutrophil is the most frequently recognized process involved in the capacity of LXs to deal with inflammation (37-40).Omega-3 polyunsaturated fatty acids are the precursors of resolvins and protectins. Resolvins are categorized into two types: D and E. "RvE1 and RvD1, like LXA4, can suppress PMN invasion and promote the phagocytosis of apoptotic neutrophils" (41-43).

Resolution of inflammation IN AD disease

Inflammation is one of the explanations put out for the complex etiology of AD. While this aspect could interact in a number of manners with other genetic, biochemical, and environmental reasons, current evidence suggests that inflammation may have a critical role in AD (13).

Inflammation's significance in the development of AD disease is becoming increasingly clear. A process known as resolution actively balances the beginning of the acute inflammatory response. Pro-resolving lipoxins are produced more often as inflammation transitions from the initiation to the resolution phase, and levels of pro-inflammatory prostaglandins and leukotrienes are initially reduced. There is growing evidence that AD affects the ability of inflammation to resolve, leading to persistent inflammation and the aggravation of disease associated with AD.

Existing research using lipoxin therapy in transgenic mice with pathology similar to AD has also produced strong preclinical evidence in favor of the involvement of poor resolution in the emergence of AD pathology. "Leukocyte recruitment, NF-B activation, superoxide production, and longer-lasting effects on the production of pro-inflammatory chemokines and cytokines are all decreased by lipoxins, especially LXA4 and its aspirin-triggered (AT) carbon-15 (15R) epimers, which are also powerful promoters of resolution".

By producing 15R epimerization intermediaries known as AT lipoxins, aspirin was discovered to alter lipoxin production, rendering it more sensitive to inactivation and further enhancing resolve signaling (44-46).

In terms of AD pathogenesis in particular, -3 FAs have been found to specifically induce many possibly beneficial implications: decreases in Aβ accumulation and Aβplaque the density alterations in Aβ ratios supported the less fibrillogenic kinds of the proteins to protect over "tau hyperphosphorylation, lowered inflammation, and improved cognitive function". Furthermore, a meta-synthesis and comprehensive review investigating the impact of -3 FAs on psychological and neurological disorders in AD research on animals demonstrated that long-term dietary supplements, which includes an average of 10% of the general life span, had been connected to decreased A levels, boosted mental processes, and decreased loss of neurons (47-49).

Resolution of inflammation IN periodontal disease

While there are numerous factors that contribute to periodontal disease, the colonization of the cavity in the mouth by bacteria that are pathogenic and their following entry into the local epithelium layer is one of the triggers that have been most important (50).

This starts an inflammatory cascade characterized by an upsurge in the synthesis of multiple mediators of inflammation and adhesion molecules, all of that in turn activate and draw in macrophages as natural killer (NK), dendritic cells (DC), and polymorphonuclear neutrophils (PMN) to the damaged area. In typical

circumstances, the microbial organisms are phagocytosed by neutrophils and macrophages, after which they go through apoptosis at the inflamed sites (23).

The elimination of cells that are apoptotic facilitates it being simpler for macrophage phenotypes to change from pro- to anti-inflammatory, that begins with the end of inflammation, a coordinated signaling mechanism that returns cell health and functioning. Yet, failure to stop the inflammatory cascade after the pathogenic stimulus has been eliminated results in persistent inflammation, which is characteristic of many illnesses connected to inflammatory disorders. While infectious microorganisms persist in spreading and are unable to be stopped by the acute immune system attack, the process of inflammatory response particularly in PD grows chronic, resulting in persistent inflammation and damage of the surrounding alveolar bone and soft tissue (51,52).

Studies on humans using low-dose aspirin and supplements of omega-3 fatty acids as an adjuvant to periodontal therapy have shown encouraging results and suggest a synergistic interaction between these medications. There haven't been any lengthy randomized clinical trials comparing the advantages of omega-3 fatty acids as an adjuvant to periodontal therapy to those of other widely used pharmaceutical drugs, such as antibiotics. Large-scale experiments investigating the benefits of RvE1 therapy in patients with periodontitis may also provide greater insight into the intricate molecular processes underlying the remission of periodontal inflammation. It is necessary to do more research to determine whether RvE1 is an appropriate treatment option for periodontitis, either on its alone or in conjunction with other regimens (53).

Conclusion

Regarding the importance of peripheral factors that are inflammation in commencing neuroimmune reactions and affecting cognitive capacities, the process linking cytokine immune systems generated by the tissues of periodontal disease to the brain system remained unexplained.

The present evidence clearly supports proinflammatory cytokines as a significant component in the etiology of periodontal disease and AD. A plausible idea is that lowering proinflammatory cytokines might be a potential technique for interfering with the illness process. Since the existence of proinflammatory cytokines is an established cause for AD, proper PD therapy or prevention may help to postpone the onset of the chronic condition. As a result, additional rigorous and higher-level research, such as RCTs, will be needed to back up these conclusions**.**

The recovery of microbiome/host balance by specific pro-resolving lipid mediator treatment shows that microbiome dysbiosis, the host hyperinflammatory phenotype, and periodontitis may all be restored.

Outlook

More study must be done to understand the specific nature of the link among AD and PD. That far long-term human research incorporating rigorous investigation of cognitive function in susceptible patients with a history of periodontal disease would be required to substantiate such relationships. Also, more research is needed to determine the cognitive improvement associated with proinflammatory cytokine modulation.

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