Review Article

Highlighting the Effect of Pro-inflammatory Mediators in the Pathogenesis of Periodontal Diseases and Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurological condition that is much more common as people get older. It may start out early or late. Increased levels of pro-inflammatory cytokines and microglial activation, both of which contribute to the central nervous system's inflammatory state, are characteristics of AD. As opposed to this, periodontitis is a widespread oral infection brought on by Gram-negative anaerobic bacteria. By releasing pro-inflammatory 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 part in both the disease processes. 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, IL-1, NSAID, periodontal disease, pro-inflammatory cytokines, resolution of inflammation, TNF α*

Background

Alzheimer's disease (AD) is a devastating neurological disease that mostly affects the elderly and is a serious health concern among geriatric patients worldwide. The prevalence of Alzheimer's disease rises dramatically with age, reaching about 50% in patients aged 85 years old.[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]

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The preponderance of new AD cases is sporadic and late-onset, and without a significant pharmaceutical breakthrough, the prevalence is expected to double by the middle of this century, eventually reaching a global prevalence of around 131.5 million.[5,6]

As the population ages and the life span increases, the prevalence of AD and periodontal disease will increase even further and is expected to affect around 14 million

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people in the next 50 years.[1,7] A decrease in the prevalence of AD and periodontal disease can be achieved by switching to newer treatment approaches that can be effective against probable risk factors for both conditions.[1]

Both Alzheimer's disease and periodontitis can have an early or late onset. Early-onset AD and periodontitis are regarded to be genetically determined, but late-onset AD and periodontitis, which affect the majority of patients, are likely to be the consequence of a combination of genetic and environmental influences. Age, diabetes, and education are all risk factors for both conditions. Moreover, periodontitis is thought to be one of the possible risk factors for Alzheimer's disease.[1,7]

The "chicken or egg first" argument may be drawn from the vast majority of cross-sectional and longitudinal association research. Is the association between Alzheimer's disease and periodontal disease just due to the Alzheimer's patient's failure to efficiently remove a dysbiotic biofilm with a daily plaque management program? Or, can the penetration of inflammatory cytokines into the brain as a result of the host's interaction with pathogenic microbiota play a role in the onset and development of Alzheimer's disease?[8,9]

There is mounting evidence that periodontitis can impact the entire body and is a risk factor for Alzheimer's disease. Hence, there may be a relationship between inflammatory mediators produced by the interaction of oral pathogens with the host and Alzheimer's disease. This might be especially significant given the age-related prevalence of chronic periodontitis and Alzheimer's disease.[10]

The steady growth in the body's pro-inflammatory condition with age supports the state of vulnerability to periodontitis and Alzheimer's disease.[11]

Inflammatory Mediators in the Pathogenesis of AD

The primary glial cell types that comprise the brain's innate immune system are astrocytes and microglia.[12] Phagocytosis is one of the immune response mechanisms and immunological surveillance carried out by microglia, the only immune-derived cells in the brain. However, astrocytes serve as antigen-presenting cells, control immunological responses by producing cytokines, and carry out many homeostatic roles in the central nervous system (CNS).[13]

Microglia and astrocyte activation appear to have a beneficial effect on Aβ clearance during the chronic phase of neuroinflammation and early AD development. Nevertheless, as the condition worsens, persistent brain stimulation of astrocytes and microglia may enhance AD pathogenesis.[14]

Studies have shown several pathways by which neuroinflammation plays a major role in the pathogenesis of AD, including astrocytes[15,16] and microglial activation,[17] as well as increases in pro-inflammatory mediators such as chemokines and cytokines.[18]

The amyloid-beta (Aβ) hypothesis has been the most established model of AD pathogenesis. It proposes that the deposition of misfolded and aggregated Aβ is a critical and the initial pathological event in AD. Several studies have shown that Aβ can activate several microglial receptors, causing the secretion of cytokines, chemokines, and reactive oxygen species.[19,20]

Inflammation may contribute to the pathogenesis of AD by two mechanisms. The first is a preliminary innate immune response to the alterations in the AD brain; inflammation is involved in the recruitment of immune cells to the site of injury as a result of the initial signaling of cytokines and chemokines and complement system activation. The second mechanism involves a minor amount of on-going inflammation in the brain, which can result in the pathogenesis of AD. This inflammation can be considered a sign of an impaired adaptive immune response and leads to chronic inflammation.[21,22]

Microglial cells can induce neuronal damage through the following processes 1- phagocytosis; 2- The release of cytokines/chemokines/prostaglandins and reactive oxygen species (ROS).

There is growing evidence that inflammatory mediators in the CNS contribute to cognitive impairment through cytokine-mediated interactions between glial cells and neurons. Moreover, it has been demonstrated that AD is associated with the upregulation of pro-inflammatory cytokines, which can initiate plaque production and enhance nerve cell degeneration. Some of these mediators include tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IFN-γ.[23,24]

The elevation of IL-1β, IL-6, and TNF-α is widely recognized as a critical component of neuro-inflammation and leukocyte recruitment to the CNS.[23]

Moreover, IL-1β and TNF-α are potent stimuli for inducible nitric oxide synthase (NOS) expression and activity in the brain and NO metabolite overflow into the cerebrospinal fluid.

TNF-α can mediate neuronal dysfunction as well as Aβ-induced disruption of the molecular mechanisms involved in memory function. Likewise, TNF-α can stimulate the accumulation of the tau proteins in neurites through induction of ROS.[25]

Recently, it was shown that individuals with severe forms of AD have higher TNF- levels when their NO levels are high. In addition, genetic and epidemiological research has linked elevated TNF α levels in the brain to an increased risk of Alzheimer's disease.[25]

Owing to the important role that inflammation plays in the development of AD, several inflammatory mediators, including TNF α, IL-1 α, and IL-1B, have been proposed as AD indicators. Furthermore, periodontitis and other conditions linked to local or systemic inflammation have been suggested as risk factors for the emergence of AD.[26]

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.[27]

In older persons with intact cognitive function, the production of pro-inflammatory cytokines by peripheral immune cells has been considered as a predictor of future risk of AD.[28]

The main mechanism is that the central microglial cells are primed by systemic inflammatory signals and antigens, which subsequently display an aggressive pro-inflammatory phenotype aggravating neuroinflammation and neurodegeneration in AD.[29]

Additionally, increased levels of plasma TNFα, IL-1, and IL-6 were observed in AD patients compared to normal patients.[30]

TNF α has also been connected to memory problems in a similar manner. An acute systemic inflammatory event and high baseline plasma TNF α 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 TNF α targeting receptor prevented memory loss brought on by amyloid.[31,32]

In individuals with AD, elevated IL-1β predicted rates of cognitive decline.[27]

Patients with elevated markers preceding baseline levels showed a greater rate of cognitive decline over a 2-month follow-up period than those who did not have elevated levels before baseline. Similarly, dementia is also considered to be a complex disorder associated with an interaction between genetics and diseases related to systemic inflammation. Elevated blood inflammatory markers predict risk for dementia and incidence of cognitive impairment. Cross-sectional and longitudinal studies have revealed dementia in subjects with poor oral health.[33]

Thus, periodontitis which leads to the presence of inflammatory molecules in systemic circulation is thought to be a definite risk factor for developing a variety of systemic diseases including AD.

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.[34] Paradoxically, tissue breakdown is also a function of the host systems that protect against certain diseases. Hence, the spatial direction of the inflammatory infiltration to the bone and periodontal tissue is a crucial factor that might establish whether the destructive effect predominates over infection management, and the involvement of pro-inflammatory mediators in the inflammatory process is crucial.[34]

Cytokines are important in a variety of physiological functions, but when they are released inappropriately, they can cause disease. The balance of pro- and anti-inflammation in periodontal disease is skewed toward pro-inflammatory activity. Interleukin-1 (IL-1) and IL-6 as well as tumor necrosis factor (TNF α) appear to play important roles in periodontal tissue destruction.[35,36]

The host tissue cells (neutrophils and monocytes) express IL-1 and -1, IL-6, TNF α, and prostanoids, eventually paving the path for greater destruction of periodontal tissues. Hence, the host reaction has a dual function that causes tissue proteolytic enzymes to express themselves excessively, ultimately causing the host to self-destruct.[37]

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 widely acknowledged and supported by data that the presence of inflammation in the brain causes cognitive impairment, such as that found in Alzheimer's disease. This inflammatory dysfunction is due to cytokine-mediated interactions between neurons and glial cells.[38,39]

Periodontitis may lead to the advancement of Alzheimer's disease as a result of the host's reaction to periodontal infections, which causes an increase in the levels of pro-inflammatory cytokines. This causes a cascade of cytokines and pro-inflammatory chemicals to be released into the systemic circulation, resulting in a systemic inflammatory load and a phase of systemic/peripheral inflammation. These pro-inflammatory chemicals can cross the blood-brain barrier (BBB) and enter the brain areas [Figure 1]. This results in the priming/activation of microglial cells and the negative consequences of neuronal injury. TNF-α, TGF-β, and chemokines (monocyte chemotactic protein, IL-8, macrophage migration inhibitory factor, and monokine generated by -interferon) have also been identified as serum and plasma biomarkers for the etiology of Alzheimer's disease.[40] The production of cytokines, particularly TNF-α, during inflammation plays a significant part in neurodegenerative illness. Gliosis, demyelination, BBB degradation, and cell death are caused by TNF-α 's exaggeration of the inflammatory process. In light of this, TNF-α is crucial to the neurodegenerative process.[39]

More recently, a mouse model with *P.gingivalis*-induced experimental periodontitis exhibited memory impairment and a significant increase in amyloid plaque loads as well as high levels of interleukin-1β and TNF-α in the brain.[41]

Resolution of Inflammation in AD and Periodontal Disease

Increased release of pro-inflammatory mediators such as prostaglandins and leukotrienes, which result in polymorphonuclear (PMN) leukocyte recruitment and monocyte-macrophage proliferation, has been well characterized as the onset of the acute inflammatory phase, which is typically brought on by trauma, infection, tissue injury, neoplasia, or other major homeostatic stressors.[42,43]

It was once thought that the acute response to inflammation passively subsided over time, but more recently, it has become clear that acute inflammation is maintained in a state of homeostatic balance by resolution, which eventually leads to the removal of recruited granulocytes and the restoration of immune profiles before activation.[44]

A lack of resolution has been linked to the development of chronic inflammation, which is involved in the etiology of several illnesses, including AD and periodontitis.[5]

To resolve inflammation, active biochemical pathways controlled by mediators that alter protein function, gene expression, and tissue-resident cells that encourage the host tissues to revert to homeostasis are necessary. Essential polyunsaturated fatty acid (PUFA)-derived lipid mediators (LMs), sometimes referred to as specialized pro-resolving mediators (SPMs), are mediators that govern this process by inducing the resolution process.[45]

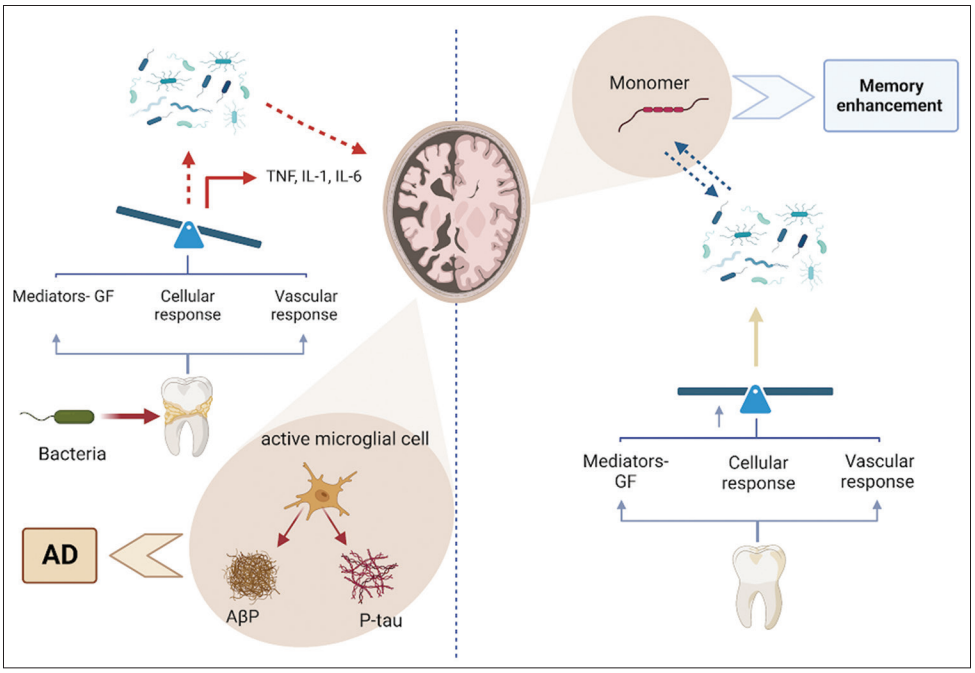

Figure 1: Periodontitis may lead to the advancement of Alzheimer's disease as a result of the host's reaction to periodontal infections, which causes an increase in the levels of proinflammatory cytokines. This causes a cascade of cytokines and pro-inflammatory chemicals to be released into the systemic circulation, resulting in a systemic inflammatory load and a phase of systemic/peripheral inflammation. These pro-inflammatory chemicals can cross the BBB and enter the brain areas. Created with Biorender.com

Many active and well-coordinated measures must be taken for inflammation to be successfully resolved. They include the cessation of neutrophil recruitment, the clearance of apoptotic neutrophils by tissue phagocytes (efferocytosis), the beginning of tissue healing, and the upregulation of regulatory or pro-resolution mediators in contrast to the increase of pro-inflammatory mediators.[46]

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 PUFA-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 resolvins 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 the vascular endothelium.[47-49]

Resolution of inflammation is not only a passive cessation of inflammation; rather, it is an active biochemical and metabolic process that is mediated by specific pro-resolving lipid mediators. Lipoxins, resolvins, and protectins are specialized pro-resolving lipid mediators. It is widely known that specific pro-resolving lipid mediators are required to reduce inflammation-related tissue damage. Receptor agonists are specialized pro-resolving lipid mediators. They pro-actively indicate the cessation of inflammation by binding to receptors that are only activated during inflammation: a feed-forward signal as opposed to non-specific inhibition. The evidence indicates that the exogenous addition of specific pro-resolving lipid mediators activates their receptors and stops chronic inflammation in instances of failure of resolution.[50-52]

The most promising pro-resolution mediators at the moment are a variety of lipid mediators made from PUFAs. They include maresin, resolvin-D, resolvin-E, protectin, and lipoxin (LX). Arachidonic acid, an omega-6 PUFA, is the source of lipoxins. LXs are made swiftly and function in either a paracrine or autocrine way. Formylpeptide receptor2/lipoxin A4 receptor (ALX/FPR2), a member of the formyl peptide receptor superfamily, is the binding site for lipoxinA4 (LXA4). The capacity of LXs to stop the recruitment of neutrophils is the most generally acknowledged mechanism implicated in the ability of LXs to resolve inflammation. Omega-3 PUFAs are the source of resolvins and protectins. Resolvins are classified into two types: D and E. RvE1 and RvD1, like LXA4, can inhibit PMN invasion and increase macrophage phagocytosis of apoptotic neutrophils.[53-55]

Resolution of Inflammation in AD

Inflammation is one of the theories put out for the multi-factorial etiology of AD. Although this component may interact in a variety of ways with other genetic, biological, and environmental causes, current research suggests that inflammation may play a pivotal role in AD.[56]

Inflammation's significance in the development of AD 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.[57]

Existing research using lipoxin therapy in transgenic mice with pathology similar to AD has also produced strong pre-clinical 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.[58]

By producing 15R epimerization products known as AT lipoxins, aspirin has been demonstrated to influence lipoxin production, making it more resistant to inactivation and further enhancing resolution signaling.[59]

In terms of Alzheimer's disease pathology, -3 FAs have been shown to specifically induce the following potentially therapeutic effects: reductions in Aβ accumulation and Aβ plaque density changes in Aβ ratios favoring the less fibrillogenic forms of the peptide protection against tau hyperphosphorylation, reduced inflammation, and improved cognitive performance. Furthermore, a systematic review and meta-analysis focusing on the impact of -3 FAs on cognition and AD pathology in AD animal models revealed that long-term supplementation, defined as at least 10% of total life span, was associated with lower A levels, improved cognition, and decreased neuronal loss.[60-62]

Resolution of Inflammation in Periodontal Disease

Although there are many causes of periodontal disease, the colonization of the oral cavity by pathogenic bacteria and their subsequent penetration into the local epithelial lining are among the triggers that are becoming best addressed.[63]

This launches an inflammatory cascade marked by an upsurge in the production of several inflammatory mediators and adhesion molecules, which together mobilize and draw in macrophages, natural killer (NK), dendritic cells (DC), and polymorphonuclear neutrophils (PMN) to the damaged region. In typical circumstances, the microbial organisms are phagocytosed by neutrophils and macrophages, after which they go through apoptosis at the inflamed sites.[35]

The removal of apoptotic cells makes it easier for macrophage phenotypes to shift from pro- to anti-inflammatory, which starts the resolution of inflammation, a coordinated signaling process that returns tissue integrity and function. 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. When pathogenic microorganisms continue to spread and cannot be stopped by the acute immune response, the inflammatory response, especially in PD, becomes chronic, leading to persistent inflammation and destruction of the surrounding alveolar bone and soft tissue.[64,65]

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 have not 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 alone or in conjunction with other regimens.[66]

The Role of Non-Steroidal Anti-Inflammatory Drugs for Treating AD and Periodontitis

Given that host inflammatory and immunological responses play critical roles in the pathogenesis of AD and periodontitis and impact treatment responses, several adjunctive strategies aimed at modulating host responses and improving the results of periodontal therapy and maintenance have been proposed.[67] Of the many pharmacological host modulators, we focused on non-steroidal anti-inflammatory drugs (NSAIDs) due to their long history and extensive use in relieving inflammation and pain and reducing platelet aggregation. NSAIDs have been routinely indicated for treating rheumatic fever and osteoarthritis and utilized for the prevention of cardiovascular events.[68] Although several efforts have been made to incorporate NSAIDs into the treatment of periodontitis, their effects on periodontal health remain poorly characterized, and concerns over the risk–benefit ratio are also raised.

Anti-Inflammatory Medications for Treating AD

NSAIDs are commonly used drugs that work by blocking the enzyme cyclooxygenase (COX), which changes arachidonic acid into prostaglandins, to relieve pain, fever, and other inflammatory processes.[67]

Clinical studies and animal models have been utilized to evaluate the use of NSAIDs for AD since the 2000s.[69,70] Studies on transgenic mice models of AD have demonstrated that therapy with ibuprofen and naproxen might prevent changes to the microglia.[33,71]

The inhibition of COX is one of the most well-established mechanisms by which NSAIDs can reduce the symptoms of AD.[72] Since COX-2 is highly expressed in the brain's degenerative cells, blocking COX may lower the chance of getting AD.[73]

There are alternative theories that suggest NSAIDs can directly interact with Aβ to stop its build-up. It has been observed that NSAIDs, including ibuprofen and indomethacin, decrease the synthesis of amyloid Aβ42 independently of COX-2 suppression.[74]

Anti-Inflammatory Medications for Treating Periodontitis

Even though biofilms are the first stage of periodontal disease, each patient has a different immunoinflammatory response and susceptibility profile. These responses affect how well each step of periodontal therapy works as well as how much periodontal tissue is destroyed locally due to the synthesis and secretion of immunological factors.[68]

Consequently, a number of host modulators have been suggested as supplements to traditional periodontal therapy. NSAIDs are the most popular and widely prescribed of these host modulators.

Their pharmacological action is predicated on cyclooxygenase (COX) inhibition.[75] It is difficult to reach a firm conclusion on the effectiveness of NSAIDs in treating periodontitis, despite the fact that several research have examined their effects, either on their own or in conjunction with non-surgical or surgical periodontal therapies. This is made worse by the fact that most disorders may be treated without the use of NSAIDs as an adjuvant because standard periodontal treatments are safe and effective in reducing inflammation and stopping tissue deterioration.[76]

Conclusion

Despite the importance of peripheral inflammatory cytokines in triggering neuroimmune responses and influencing cognitive functioning, the mechanism connecting cytokine immune responses from the periodontium to the brain remains unknown.

The present evidence clearly supports pro-inflammatory cytokines as a significant component in the etiology of periodontal disease and Alzheimer's disease. A plausible idea is that lowering pro-inflammatory cytokines might be a potential technique for interfering with the illness process. Since the existence of pro-inflammatory cytokines is a known risk factor for Alzheimer's disease, 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.

Additionally, possible AD therapies that restore the inflammatory phenotype, such as the use of NSAIDs, are being extensively researched and developed.

Although various studies have been conducted to study the effects of NSAIDs on the treatment of periodontitis, either alone or as adjuncts to non-surgical or surgical periodontal therapies, drawing a firm conclusion on their efficacy remains difficult. Given the costs and benefits, systemic or local use of NSAIDs as an adjuvant to traditional periodontal therapy is not recommended.

Outlook

Further research is required to identify the exact nature of the relationship between 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 pro-inflammatory cytokine modulation.

List of abbreviations

AD: Alzheimer's disease
CNS: Central nervous system
TNF α: Tumor necrosis factor α
IL-1β: Interleukin 1β
IL-8: Interleukin 8
NSAID: Non-steroidal anti-inflammatory drug
Aβ: amyloid-beta
ROS: Reactive oxygen species
Interleukin-6: IL-6
NOS: Nitric oxide synthase
TGF-β: Transforming growth factor-β
PGE2: Prostaglandin E2
PUFA: Polyunsaturated fatty acid
SPMs: Specialized pro-resolving mediators
LMs: lipid mediators
ICAM-1: Intercellular adhesion molecule 1
PMN: Polymorphonuclear neutrophils
AT: Aspirin-triggered
NK: Natural killer
DC: Dendritic cells
PD: Periodontal disease
COX: Cyclooxygenase
BBB: Blood-brain barrier.

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Conflicts of interest

There are no conflicts of interest.

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