REVIEW ARTICLE

# Alzheimer's disease and periodontitis – an elusive link

Abhijit N. Gurav

Professor Department of Periodontics
Tatyasaheb Kore Dental College & Research Centre

**Article received:** 01/16/13
**Accepted for publication:** 03/27/13

**Correspondence:**
Department of Periodontics
Tatyasaheb Kore Dental College &
Research Centre
New Pargaon
Kolhapur-416137
Maharashtra State
INDIA
Phone +91 230 2477081
Fax +91 230 2477082
dr_abhijitg@yahoo.co.in

http://dx.doi.org/10.1590/1806-9282.60.02.015

**Conflict of interest:** none

## Summary

Alzheimer's disease is the preeminent cause and commonest form of dementia. It is clinically characterized by a progressive descent in the cognitive function, which commences with deterioration in memory. The exact etiology and pathophysiologic mechanism of Alzheimer's disease is still not fully understood. However it is hypothesized that, neuroinflammation plays a critical role in the pathogenesis of Alzheimer's disease. Alzheimer's disease is marked by salient inflammatory features, characterized by microglial activation and escalation in the levels of pro-inflammatory cytokines in the affected regions. Studies have suggested a probable role of systemic infection conducing to inflammatory status of the central nervous system. Periodontitis is common oral infection affiliated with gram negative, anaerobic bacteria, capable of orchestrating localized and systemic infections in the subject. Periodontitis is known to elicit a "low grade systemic inflammation" by release of pro-inflammatory cytokines into systemic circulation. This review elucidates the possible role of periodontitis in exacerbating Alzheimer's disease. Periodontitis may bear the potential to affect the onset and progression of Alzheimer's disease. Periodontitis shares the two important features of Alzheimer's disease namely oxidative damage and inflammation, which are exhibited in the brain pathology of Alzheimer's disease. Periodontitis can be treated and hence it is a modifiable risk factor for Alzheimer's disease.

**Key words**: Alzheimer's disease, periodontitis, cytokines, systemic inflammation, periodontal pathogen.

## Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly age group and a major health problem in the geriatric subjects worldwide. The incidence of AD rises significantly with age, reaching almost 50% in subjects aged 85 years.[1] AD is seen as an interaction between genetic and environmental factors. The hallmark of AD is progressive cognitive impairment with impaired judgment and decision making, followed by psycho-behavioral disturbances and language disability.[2] Periodontitis is the most common oral infection afflicting the human race. Prevalent worldwide, periodontitis is the major cause for tooth loss in adults worldwide. The present review elucidates the enigmatic link between AD and periodontitis, showcasing the pathophysiology and possible implications of the association. This review is prepared by screening the PubMed database, utilizing keywords like "Alzheimer's disease", "periodontitis", "cytokines", "systemic inflammation" and "periodontal pathogen." Systematic reviews, meta-analysis and original articles pertaining to the subject from 1994 to 2012, were referred. Human and animal studies published in english were considered.

## Pathogenesis of Alzheimer's disease

AD is an age associated complex neurodegenerative disorder with multiple etiologies for initiation and progression. However, till date there is no confirmed or accepted model which can provide optimal explanation for the complex pathophysiology of this desolating disorder. The most significant hallmark of this disorder is the formation of extracellular amyloid β-peptide (AβP) plaques and intraneuronal neurofibrillary tangles (NFTs) of hyper-

phosphorylated tau protein, followed by consequent loss of neuronal synapses and neuronal degeneration. This leads to diminution of essential neurotransmitters.[3]

Enhanced expression of the amyloid precursor protein (APP) gene caused as a result of genetic aberration may be a risk factor for late-onset AD. Apolipoprotein epsilon4 (APOEε4) allele is genetically linked to majority of the AD cases.[4]

AβP, the main component of amyloid plaques is derived from APP by proteolytic cleavage. Studies corroborate the hypothesis that APP and AβP are instrumental in the pathogenesis of AD.[2] The NFTs are constituted of hyperphosphorylated forms of the microtubule-associated protein tau. The microtubule-associated tau protein is responsible for the stability of microtubules in neurons. Hyperphosphorylated tau is insoluble with low affinity for microtubules, jeopardizing the microtubule stabilization, thus conducing to synaptic dysfunction and neurodegeneration. Hyperphosphorylation of tau takes place as a result of inflammation, oxidative stress, up-regulation of tau kinases and down-regulation of phosphatases.[5] However studies have revealed the interplay of other factors apart from the characteristic AβP plaques and intraneuronal NFTs for the complete evolution of AD.[6] AβP exerts detrimental effects on the neurovascular endothelial cells, either by direct action or causing local inflammation. Inflammation leads to AβP formation in the cerebral microvasculature and AβP, in turn, stimulates the release of pro-inflammatory mediators.[7] Initially, AD was conceived as a disorder related to the augmentation in the synthesis and decline in the degradation of AβP. Now, impaired clearance is also stated as a co-factor. This hypothesis has been proposed as the "amyloid cascade hypothesis" of AD, with APP playing a pivotal role.[8] In AD, the neuroinflammation is significantly exaggerated. It is hypothesized that neuroinflammation may be a result of pro-inflammatory cytokines, reactive oxygen and nitrogen species, instrumental in activation of microglia and abetting the formation of NFTs.[9,10] AβP plaques in AD affected brains are closely affiliated with reactive astrocytes and activated microglial cells, which exhibit exuberant expression of cytokines and acute-phase proteins.[11] Microglia cells are mononuclear phagocytes present in the brain, committed to thwart any noxious injury within the central nervous system and achieve brain homeostasis. In health, microglial cells maintain a neuroprotective function by clearing the AβP plaques.[12]

They also express several neurotrophic factors, such as insulin-like growth factor (IGF)-1, brain-derived neurotrophic factor, transforming growth factor-β and nerve growth factor. In states of peripheral or systemic inflammation, the molecular and cellular components extend the inflammatory signals to the brain via different pathways. Under normal conditions, the inflammatory response is suitably regulated to avoid uncontrolled inflammatory damage.[13] However, the normal regulatory mechanisms may become deficient with aging and genetic predisposition.[14,15] Thus, a sustained inflammatory response persists. During these states, the microglial cells in the brain are programmed to switch their phenotypes to produce neurotoxic substances in event of exposure to the systemic inflammatory signals. Thus, instead of confronting with a protective response to these systemic inflammatory signals an exaggerated response is elicited by the diseased microglia, contributing to the pathogenesis of AD. The "fired up" microglia changes its morphology and releases a number of cell antigens. These are referred to as 'activated microglia'. Activation of microglia results in expression of various pro-inflammatory factors. The uncontrolled release of these factors can induce neural damage. The microglial function may be likened to a "double-edged sword" being either damaging or protective depending on the context.[13,16] Chronic inflammation and cytokine up-regulation conduces to tau hyperphosphorylation in experimental mice model of AD.[17] It has been observed that, chronic lipopolysaccharide (LPS)-induced neuroinflammation ensues in the elevated levels of intraneuronal AβP in transgenic mice. This may contribute to the deterioration of AD affected brain.[18,19]

## Periodontitis – a low grade systemic disease

Periodontitis is a polymicrobial inflammatory disorder of the tooth investing tissues, resulting from microorganisms residing within the dental plaque. Periodontitis is characterized by bleeding and purulent discharge from the gums, progressive deepening of gingival sulcus (referred as pocket formation), oral halitosis, spacing between the teeth and mobility of teeth in advanced stages.[20] Dental plaque, the principal cause of periodontitis, exists in the form of biofilm. The gram negative and anaerobic species colonize in the periodontal pocket milieu. The predominant periodontal pathogens involved in periodontitis are *Aggregatibacter actinomycetemcomitans* (Aa), *Porphyromonas gingivalis* (Pg), *Prevotella intermedia* (Pi), *Fusobacterium nucleatum* (Fn), *Tannerella forsythensis* (Tf), *Eikenella corrodens* (Ec) and *Treponema denticola* (Td).[21,22] The present model to explain the pathogenesis of periodontitis was proposed by Page and Kornman (figure 1).[23] The periodontal pathogenic flora releases an array of pro-

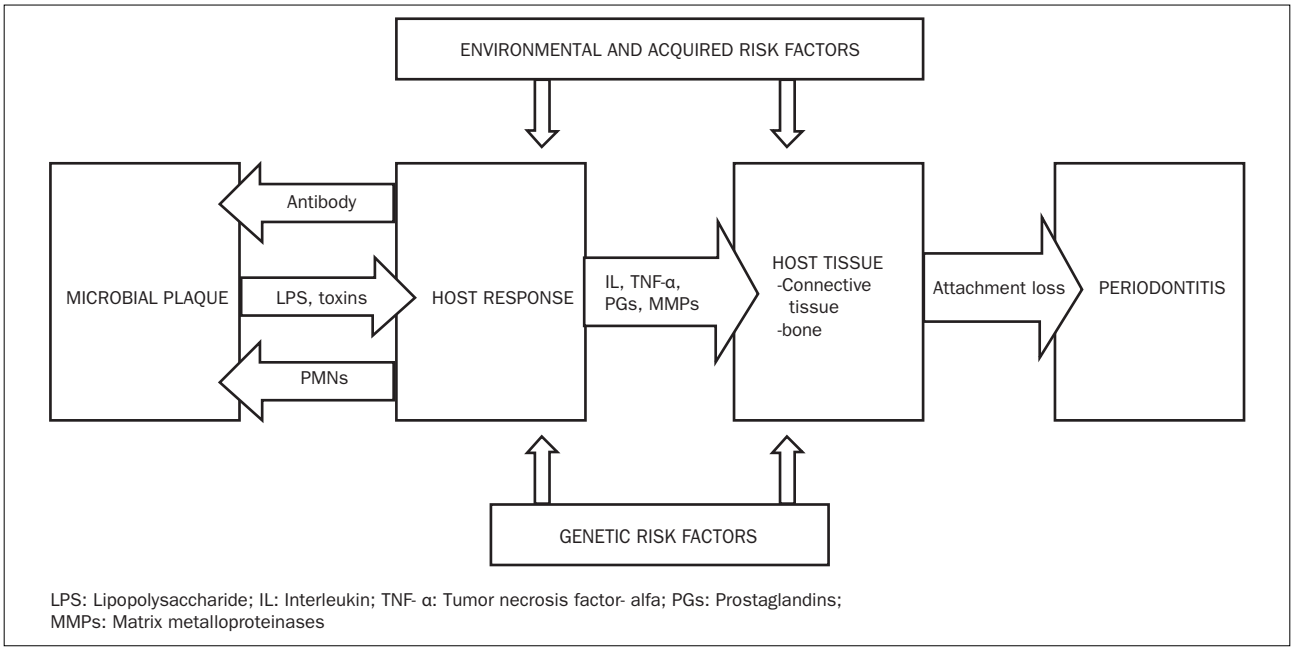


**FIGURE 1** Pathogenesis of periodontitis (Page and Kornman model, 1997).

teolytic enzymes, which are implemental in destruction of soft and hard tissues supporting the teeth. The gram negative bacterial LPS also adds to the tissue destruction by amplifying the host response, resulting in the expression of pro-inflammatory factors like interleukin (IL)-1α and -1β, IL-6, tumor necrosis factor (TNF) – α, prostanoids, matrix metalloproteinases (MMP), by the host tissue cells.[24] Host defense cells like neutrophils, monocytes secrete cytokines such as IL-1α and 1β, TNF - α in the diseased periodontal site. These cytokines act as crucial factors in host mediated bone resorption and periodontal tissue destruction.[25] Host response in periodontal disease may act as the diabolical "double-edged sword" leading to self destruction, due to the exaggerated expression of tissue proteolytic enzymes.[26] The ulcerated periodontal pocket lining furnishes a portal access for the bacteria and their noxious products, into the systemic circulation. It is reported that the total surface area of the ulcerated periodontal pocket lining in patient with severe periodontitis is approximately 15-20 $cm^2$.[27] In periodontitis, the locally produced cytokines and pro-inflammatory products are actually streamed through the ulcerated periodontal pocket lining, into systemic circulation. This alters the character of periodontitis from a local disease to that of a systemic disorder, capable of sustaining "low grade systemic inflammation."[28] This low grade inflammation is conceived to perturb the general systemic health and exasperate other systemic disorders. Thus periodontitis can be marked as a "low grade systemic disease". Studies have isolated a number of systemic inflammatory biomarkers, reiterating a positive association of periodontitis with systemic inflammation. Surrogate markers of host response against periodontal infection like cytokines, chemokines, inflammation markers, anti-phospholipid antibodies, antibodies to periodontal pathogens can be demonstrated in serum.[27,29]

The concept of "periodontal medicine" associates periodontitis as a risk factor with a large number of systemic disorders.[30] Periodontal inflammation and atherosclerotic cardiovascular diseases (ACD) display a concomitant increase in the levels of inflammatory systemic markers like acute phase reactants, interleukins and TNF-α. Meta-analyses have concluded that subjects with periodontitis are at a serious risk of ACD.[31,32]

## AD and periodontitis – a plausible link

The exact mechanism involved in the pathogenesis of AD is still unknown. Inflammation is known to play a pivotal role in this process. It is proposed that periodontitis can lead to progression of AD by two probable mechanisms (figure 2):

- Periodontitis preceding systemic inflammation/infection
- Bacterial and viral influence

According to the first mechanism, periodontal pathogens and the host response elevate the levels of pro-inflammatory cytokines. An array of cytokines and pro-in-

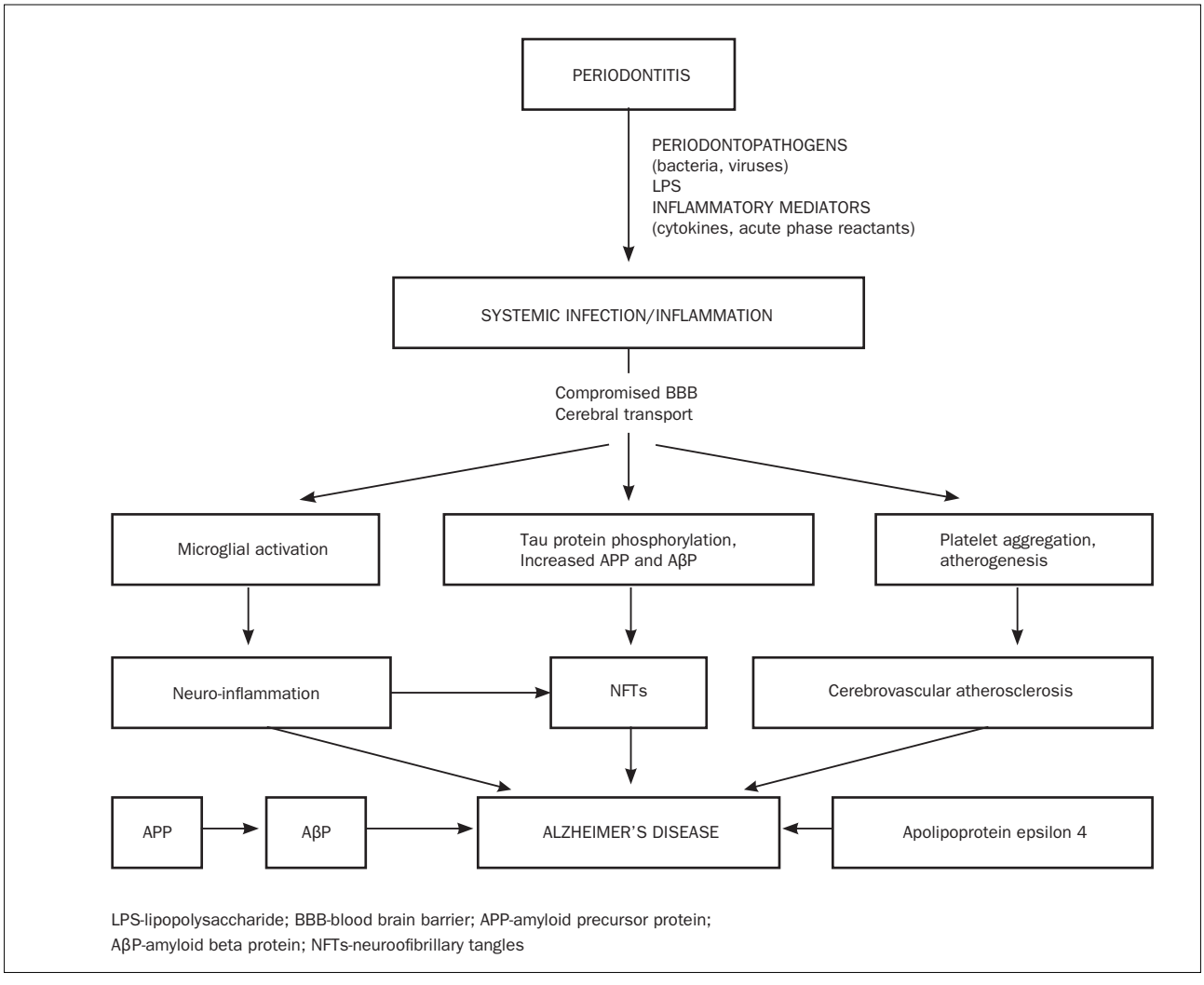


**FIGURE 2** Possible pathways for the pathogenesis of Alzheimer's disease.

flammatory agents are spurted out in systemic circulation adding to the systemic inflammatory burden. Thus, periodontitis may produce a state of systemic/peripheral inflammation. These pro-inflammatory molecules can compromise the blood brain barrier (BBB) and gain access to the cerebral regions.[33] This may result in priming/activation of microglial cells and the adverse repercussions leading to neuronal damage.

The second mechanism may involve invasion of the brain by bacteria and viruses residing in the dental plaque biofilm. This can occur directly through cerebral transport via blood stream or via peripheral nerves.[34] There is appreciable evidence blaming the inflammatory mechanisms within the central nervous system for the cognitive impairment, as that presented in AD. This involves cytokine arbitrated interactions between neurons and glial cells. Various cytokines consisting of interleukin family, TNF- α, Transforming Growth Factor- β, chemokines (Monocyte Chemotactic Protein, IL-8, Macrophage Migration Inhibitory Factor, Monokine Induced by γ-Interferon, Fractalkine) have been implicated as serum and plasma biomarkers for pathogenesis of AD.[35] TNF- α expression is up-regulated in AD and it is considered to be the crucial inflammatory cytokine, regulating cellular cascade of events in neuroinflammatory response. TNF- α exacerbates gliosis, demyelination, inflammation, blood-brain-barrier deterioration and cell death. Thus, TNF- α plays a pivotal role in the neurodegenerative disease process.[36,37] Studies on mice models have revealed salutary effects of anti-inflammatory agents in the amelioration of neuroinflammation and amyloid plaque deposition. A significant decrease in the levels of IL-1β and glial fibrillary acidic protein levels as well as diminished plaque load was observed in mice treated with non steroidal anti-inflammatory agent.[38,39]

The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), corroborates the hypothesis that the beneficial role of anti-inflammatory drugs is evident only in the early, asymptomatic, phases of the disease.[40] Inflammation could serve as a connecting link between periodontitis and AD. However there are no animal studies, specifically addressing the causal relationship of periodontal inflammation to AD, in the literature. Dementia may be designated as a complex disorder associated with an interaction between genetics and diseases related to systemic inflammation, including diabetes mellitus and environmental factors like smoking. Cross-sectional and longitudinal studies have revealed dementia in subjects with poor oral health.[41-43]

Rai *et al.* observed statistically significant difference between patients and controls, concerned to the clinical periodontal parameters like gingival inflammation, dental plaque, bleeding on probing and probing pocket depth. Total counts of WBCs, neutrophils, thrombocytes and levels of pro-inflammatory markers like CRP, MMP-8, MMP-9 and TNF-α were significantly elevated in subjects with dementia and periodontitis in contrast to healthy individuals serving as controls. RBC counts, total IGF-1 and Hb levels were diminished in subjects with dementia and periodontitis, in comparison to healthy control subjects. However, these parameters scored significantly higher in dementia as compared to periodontitis patients. An inverse relation was noted in the levels of TNF- α, MMP-8, MMP-9 and CRP levels compared to free IGF-1 concentrations.[45] There is a lack of direct clinical evidence for a causal relationship between periodontitis and AD. However, studies have observed that increased systemic/peripheral inflammation can be a contributory risk factor for AD.[45-48]

## Role of periodontal pathogens in AD

Periodontal pathogens in periodontitis like Aa, Pg, Pi, Tf, Fn are tissue invasive.[49,50] This property enables the pathogens to escape from the extracellular host defense system and replicate in the host tissues. The spirochetal species in the periodontal plaque possess a wide range of virulence factors aiding in confronting with the host defense mechanisms and enhancing its ability to invade the periodontal host tissues.[51] Spirochete plaques or masses in the brain resemble senile plaques of AD.[52]

Riviere *et al.* isolated spirochetal species like Td, *Treponema pectinovorum*, *Treponema vincentii*, *Treponema amylovorum*, *Treponema maltophilum*, *Treponema medium* and *Treponema socranskii* from the brains of AD subjects, utilizing specific PCR. Td was isolated in 14 of 16 AD subjects and 4 of 18 non AD subjects. Molecular and immunological techniques endorsed the existence of Palladium species in trigeminal ganglion specimen and cortex of AD affected subjects. AD brain specimens depicted more Treponema species in comparison to control groups. It is speculated that Treponema from oral cavity must have gained access to the brain cortex via the trigeminal nerve.[53] A significant association has been displayed between spirochetes and AD. Spirochetes were detected in the brain in 93.7% of AD cases and in 33.3% of controls. Borrelia burgdorferi was isolated 13 times more frequently in AD cases than in controls. Considering all the studies, involving spirochetal species detected in the brain, it can be reasoned that the frequency of spirochetes exceeds more than eight times higher in AD cases (90/131; 68.7%) than in control groups (6/71; 8.41%). The spirochetes may nurture a perpetual infective and inflammatory process evoking neuronal damage and dysfunction.[52,54] Study subjects with elevated levels of Pg antibodies in the serum had significantly greater odds of cognitive impairment. This finding was constant even after adjusting for the potential socio-demographic and vascular confounders. Nevertheless, the association of cognitive impairment with antibodies to Aa was weak.[55] In a longitudinal study, subjects with AD and moderate cognitive impairment (MCI) showed a significant increase in the levels of serum antibodies to Pi and Fn at the baseline, earlier to the diagnosis of the neurological deficit. The subjects with AD demonstrated significantly higher level of antibody to Td and Pg observed at the baseline. The sera analysis of these subjects was carried out before the diagnosis of AD or MCI.[56]

Herpes simplex virus type 1(HSV-1) is a common neurotropic virus that infects elderly subjects. HSV-1 is shown to be present in the brain of AD subjects. A causal role was attributed to this virus for triggering AD. Studies have noticed HSV-1 DNA in the brain of AD subjects.[57,58] Polymerase chain reaction (PCR) technique has demonstrated HSV-1 DNA in the brains of large number of elderly individuals, with or without AD. This was less conspicuous in younger subjects, serving as controls.[59] Wozniak *et al.* utilized Enzyme-linked Immunosorbent Assay (ELISA) to isolate antibodies to HSV-1 in the CSF of AD patients. Although the occurrence of anti-HSV-1 antibodies was significantly higher in AD patients than in younger controls, there was a lack of significant difference between the AD and age-matched control groups.[60] Letenneur *et al.* observed an additional presence of IgM along with IgG in the sera of 512 elderly patients, initially free of dementia. In this prospective study, during 14 years of follow up, 77 cases of AD were diagnosed. Sub-

jects nurturing IgM displayed a significantly higher risk of developing AD. The presence of IgM is indicative of active primary infection or reactivation of the viral infection. Thus, the authors concluded a correlation between reactivation of HSV-1 seropositivity and AD.[61] Viruses could be directly implicated in the pathogenesis of AD. HSV possesses glycoprotein structure that mimics the amino acid sequence of AβP and tau protein and may accumulate in the brain like AβP.[62] It was noted that HSV-1 is capable of interfering with APP metabolism and may impart to AD development.[63] HSV-1 infection is also a predisposing factor for AD in subjects with the APOEε4 allele.[64]

## Discussion

Cognitive disorders like AD have escalated steeply in the population of developed countries. This trend is observed at an alarming proportion in developing nations.[65]

The commonly accepted hypothesis for this disorder is the excessive accretion of AβP, including accumulation of abnormally phosphorylated tau proteins in the brain of the affected individuals. Neuroinflammation is a principal factor for the pathogenesis of AD. Systemic inflammation is instrumental in exacerbation of the neuronal degeneration, orchestrated by the activation of primed microglia.[66] Chronic periodontal inflammation, in periodontitis serves as a perennial source for the up-regulated levels of systemic pro-inflammatory factors. Periodontitis is a polymicrobial infection, characterized by the presence of various bacteria and viruses in the periodontal pocket milieu.[67,21] These agents, along with their products are capable of compromising the BBB and entering the brain. In the brain, these agents can exert the adverse effects either directly or indirectly by affecting the vascular integrity (figure 2). The brain invading spirochetal species can perpetuate a constant chronic inflammatory process operated by activation of the innate immune responses, involving the various signaling pathways, resulting in neuronal degeneration. Viruses, particularly HSV, can access the brain via blood stream or nerve fibers. Latent viruses may be reactivated by stress and inflammation. Pg is known to express factors responsible for platelet aggregation and induce atheromatous changes. This may contribute to the pathogenesis of atherosclerotic vascular diseases, conducting for cognitive impairment and AD.[68-71] Recent literature has referred to the link between genetic polymorphisms, and progression of periodontal disease. Periodontitis susceptible subjects harbor a hyper-inflammatory phenotype. In response to antigenic stimulus, these subjects exhibit a multifold expression of pro-inflammatory mediators. Gene polymorphism involved in periodontal inflammation could be a conceivable nexus between periodontitis and AD.[72,73] It is proposed that inflammation may act as an elusive link between periodontitis and pathogenesis of AD. Till date there is no evidence of a causal relationship between periodontitis and AD. Periodontitis can intensify the systemic bioburden and contribute to a "low grade systemic inflammation". It may be accounted as one of the possible risk factors for perpetuating the neurodegenerative process in AD.

## Conclusion

AD involves a complex pathophysiology; the exact etiopathology of which is unknown. It is proposed that inflammation could be operating as the central mechanism. Both, AD and periodontitis share the same characteristic features of chronicity with inflammation as the common link between them. Presently, studies addressing the role of periodontitis in cognitive function are limited. Systematic, multicentric longitudinal studies, with large sample sizes, should be carried out to scrutinize the association between AD and periodontitis. Periodontitis may lead to exacerbation and share risk factors with cognitive impairment related disorders. Interventional studies should be carried out to evaluate a potential benefit in periodontitis subjects with mild cognitive disorders. Levels of pro-inflammatory mediators can be de-escalated with periodontal treatment, abbreviating systemic inflammation. Presently, it may be stated that periodontitis may pose as a potential risk factor for the development of AD. An insufficient body of evidence based literature fails to endorse a causal relationship. Subjects, particularly in the geriatric category should be strongly motivated and frequent visits for periodontal maintenance should be duly emphasized. The dental professional and neurologist need to co-ordinate consistently regarding the methodical management of geriatric patients.


## Resumo

A doença de Alzheimer e periodontite - um esquivo *link*

A doença de Alzheimer é uma proeminente causa e a forma mais comum de demência. Caracteriza-se clinicamente por uma progressiva diminuição da função cognitiva, que tem início com a deterioração da memória. A exata etiologia e o mecanismo fisiopatológico da doença de Alzheimer ainda não são totalmente compreendidos. No entanto, postula-se que a neuroinflamação desempenhe

um papel crucial na patogênese da doença de Alzheimer. A doença de Alzheimer é caracterizada por importantes características inflamatórias, assinalada pela ativação microglial e escalada dos níveis de citocinas pró-inflamatórias nas regiões afetadas. Estudos têm sugerido um provável papel de infecção sistêmica imbuída de estado inflamatório do sistema nervoso central. Periodontite é uma infecção oral comum associada a germes Gram-negativos, anaeróbios, capaz de orquestrar infecções localizadas e sistêmicas no paciente. É conhecida por suscitar um "baixo grau de inflamação sistêmica" pela liberação de citocinas pró-inflamatórias na circulação sistêmica. Esta revisão elucida o possível papel da periodontite no agravamento da doença de Alzheimer e pode ter o potencial de afetar o início e a progressão da doença de Alzheimer. Periodontite partilha as duas importantes características da doença de Alzheimer: dano oxidativo e inflamação, que estão presentes na patologia do cérebro com doença de Alzheimer. Periodontite pode ser tratada e, portanto, é um fator de risco modificável para a doença de Alzheimer.

**Unitermos:** doença de Alzheimer, periodontite, citocinas, inflamação sistêmica, patógeno periodontal.

## References


1. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al.. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366:2112-7.
2. Galimberti D, Scarpini E. Progress in Alzheimer's disease. J Neurol. 2012;259:201-11.
3. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet. 2006;368:387-403.
4. Bertram L, Lill CM, Tanzi RE. The genetics of Alzheimer disease: back to the future. Neuron. 2010;68:270-81.
5. Lee YJ, Han SB, Nam SY, Oh KW, Hong JT. Inflammation and Alzheimer's disease. Arch Pharm Res. 2010;33:1539-56.
6. Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, et al.. Long-term effects of Aβ42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet. 2008;372:216-23.
7. Li M, Shang DS, Zhao WD, Tian L, Li B, Fang WG, et al.. Amyloid beta interaction with receptor for advanced glycation end products up-regulates brain endothelial CCR5 expression and promotes T cells crossing the blood-brain barrier. J Immunol. 2009;182:5778-88.
8. Claeysen S, Cochet M, Donneger R, Dumuis A, Bockaert J, Giannoni P. Alzheimer culprits: cellular crossroads and interplay. Cell Signal. 2012;24:1831-40.
9. Eikelenboom P, Veerhuis R, Scheper W, Rozemuller AJ, van Gool WA, Hoozemans JJ. The significance of neuroinflammation in understanding Alzheimer's disease. J Neural Transm. 2006;113:1685-95.
10. Arnaud L, Robakis NK, Figueiredo-Pereira ME. It may take inflammation, phosphorylation and ubiquitination to 'tangle' in Alzheimer's disease. Neurodegener Dis. 2006;3:313-9.
11. Licastro F, Candore G, Lio D, Porcellini E, Colonna- Romano G, Franceschi G, et al.. Innate immunity and inflammation in ageing: a key for understanding age related diseases. Immun Ageing. 2005;2:8.
12. Fetler L, Amigorena S. Neuroscience. Brain under surveillance: the microglia patrol. Science. 2005;309:392-3.
13. Weitz TM, Town T. Microglia in Alzheimer's disease: it's all about context. Int J Alzheimers Dis. 2012; 2012:314185.
14. Schram MT, Euser SM, de Craen AJ, Witteman JC, Frolich M, Hofman A, et al.. Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc. 2007;55:708-16.
15. Arosio B, Trabattoni D, Galimberti L, Bucciarelli P, Fasano F, Calabresi C, et al.. Interleukin-10 and interleukin-6 gene polymorphisms as risk factors for Alzheimer's disease. Neurobiol Aging. 2004;25:1009-15.
16. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. Nat Rev Immunol. 2007;7:161-7.
17. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J Neurosci. 2005;25:8843-53.
18. Lee JW, Lee YK, Yuk DY, Choi DY, Ban SB, Oh KW, et al.. Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J Neuroinflammation. 2008;5:37.
19. Tan ZS, Seshadri S. Inflammation in the Alzheimer's disease cascade: culprit or innocent bystander? Alzheimers Res Ther. 2010;2:6.
20. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005;366:1809-20.
21. Socransky SS, Haffajee AD. Periodontal microbial ecology. Periodontol 2000. 2005;38:135-87.
22. Filoche S, Wong L, Sissons CH. Oral biofilms: emerging concepts in microbial ecology. J Dent Res. 2010;89:8-18.
23. Page RC, Kornman KS. The pathogenesis of human periodontitis: An introduction. Periodontol 2000. 1997;14:9-11.
24. Ren L, Jiang, ZQ, Fu Y, Leung WK, Jin LJ. The interplay of lipopolysaccharide-binding protein and cytokines in periodontal health and disease. J Clin Periodontol. 2009;36:619-26.
25. Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol. 2008;79:1585-91.
26. Preshaw PM, Taylor JJ. How has research into cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis? J Clin Periodontol. 2011;38:60-84.
27. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol. 2005;76:2106-15.
28. D'Aiuto F, Graziani F, Tetè S, Gabriele M, Tonetti MS. Periodontitis: from local infection to systemic diseases. Int J Immunopathol Pharmacol. 2005;18:1-11.
29. Pussinen PJ, Paju S, Mäntylä P, Sorsa T. Serum microbial- and host-derived markers of periodontal diseases: a review. Curr Med Chem. 2007;14:2402-12.
30. Pizzo G, Guiglia R, Lo Russo L, Campisi G. Dentistry and internal medicine: from the focal infection theory to the periodontal medicine concept. Eur J Intern Med. 2010;21:496-502.
31. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med. 2008;23:2079-8.
32. Azarpazhooh A, Tenenbaum HC. Separating fact from fiction: use of high-level evidence from research syntheses to identify diseases and disorders associated with periodontal disease. J Can Dent Assoc. 2012;78:c25.
33. Lossinsky AS, Shivers RR. Structural pathways for macromolecular and cellular transport across the blood brain barrier during inflammatory conditions. Review. Histol Histopathol. 2004;19:535-64.
34. Kamer AR, Dasanayake AP, Craiga RG, Glodzik-Sobanskac L, Bryc M, de Leon MJ. Alzheimer's disease and peripheral infections: the possible contribution from periodontal infections, model and hypothesis. J Alzheimers Dis. 2008;13:437-49.
35. Lee KS, Chung JH, Choi TK, Suh SY, Oh BH, Hong CH. Peripheral cytokines and chemokines in Alzheimer's disease. Dement Geriatr Cogn Disord. 2009; 28:281-7.
36. Park KM, Bowers WJ. Tumor necrosis factor-alpha mediated signaling in neuronal homeostasis and dysfunction. Cell Signal. 2010;22:977-83.
37. Montgomery SL, Bowers WJ. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. J Neuroimmune Pharmacol. 2012;7:42-59.
38. Yan Q, Zhang J, Liu H, Babu-Khan S, Vassar R, Biere AL, et al.. Anti-inflammatory drug therapy alters β-amyloid processing and deposition in an animal model of Alzheimer's disease. J Neurosci. 2003;23:7504-9.
39. Heneka MT, Sastre M, Dumitrescu-OzimekL, Hanke A, Dewachter I, Kuiperi C, et al.. Acute treatment with the PPARγ agonist pioglitazone and ibuprofen

reduces glial inflammation and Aβ1-42 levels in APPV717I transgenic mice. Brain. 2005;128:1442-53.
40. Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Ashe KH, et al.. ADAPT Research Group. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. Alzheimers Dement. 2011;7:402-11.
41. Ship JA, Puckett SA. Longitudinal study on oral health in subjects with Alzheimer's disease. J Am Geriatr Soc. 1994;42:57-63.
42. Weyant RJ, Pandav RS, Plowman JL, Ganguli M. Medical and cognitive correlates of denture wearing in older community-dwelling adults. J Am Geriatr Soc. 2004;52:596-600.
43. Arrivé E, Letenneur L, Matharan F, Laporte C, Helmer C, Barberger-Gateau P, et al.. Oral health condition of French elderly and risk of dementia: a longitudinal cohort study. Community Dent Oral Epidemiol. 2012;40:230-8.
44. Rai B, Kaur J, Anand SC. Possible relationship between periodontitis and dementia in a North Indian old age population: a pilot study. Gerodontology. 2012;29:e200-5.
45. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, Van Swieten JC, et al.. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol. 2004;61:668-72.
46. Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, et al.. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. Neurology. 2007;68:1902-8.
47. Bermejo P, Martín-Aragón S, Benedí J, Susín C, Felici E, Gil P, et al.. Differences of peripheral inflammatory markers between mild cognitive impairment and Alzheimer's disease. Immunol Lett. 2008;117:198-202.
48. Bonotis K, Krikki E, Holeva V, Aggouridaki C, Costa V, Baloyannis S. J Neuroimmunol. 2008;193:183-7.
49. Dogan S, Gunzer F, Guenay H, Hillmann G, Geurtsen W. Infection of primary human gingival fibroblasts by porphyromonas gingivalis and Prevotella intermedia. Clin Oral Investig. 2000;4:35-41.
50. Gena D, Tribble, Richard J, Lamont. Bacterial invasion of epithelial cells and spreading in periodontal tissue. Periodontol 2000. 2010;52:68-83.
51. Visser MB, Ellen RP. New insights into the emerging role of oral spirochaetes in periodontal disease. Clin Microbiol Infect. 2011;17:502-12.
52. Miklossy J. Emerging roles of pathogens in Alzheimer disease. Expert Rev Mol Med. 201;13:e30.
53. Riviere GR, Riviere KH, Smith KS. Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. Oral Microbiol Immunol. 2002;17:113-8.
54. Miklossy J. Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation. 2011;8:90.
55. Noble JM, Borrell LN, Papapanou PN, Elkind MSV, Scarmeas Wright CB. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES –III. J Neurol Neurosurg Psychiatry. 2009;80:1206-11.
56. Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, et al.. Serum antibodies to periodontal pathogens are risk factor for Alzheimer's disease. Alzheimers Dement. 2012;8:196-203.
57. Itzhaki RF, Wozniak MA. Herpes simplex virus type 1 in Alzheimer's disease: the enemy within. J Alzheimer's Dis. 2008;13:393-405.
58. Itzhaki R, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet. 1997;349: 41-4.
59. Jamieson GA, Maitland NJ, Wilcock GK, Craske J, Itzhaki RF. Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. J Med Virol. 1991;33:224-7.
60. Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF. Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. J Med Virol. 2005;75:300-6.
61. Letenneur L, Pérès K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, et al.. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PLoS One. 2008;3:e3637.
62. Cribbs DH, Azizeh BY, Cotman CW, LaFerla FM. Fibril formation and neurotoxicity by a herpes simplex virus glycoprotein B fragment with homology to the Alzheimer's A beta peptide. Biochemistry. 2000;39:5988–94.
63. Shipley SJ, Parkin ET, Itzhaki RF, Dobson CB. Herpes simplex virus interferes with amyloid precursor protein processing. BMC Microbiol. 2005;5:48-55.
64. Lin WR, Shang D, Wilcock GK, Itzhaki RF. Alzheimer's disease, herpes simplex virus type 1, cold sores and apolipoprotein E4. Biochem Soc Trans. 1995;23:594S.
65. Nitrini R, Bottino CM, Albala C, Custodio Capuñay NS, Ketzoian C, Llibre Rodriguez JJ, et al.. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. Int Psychogeriatr. 2009;21:622-30.
66. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al.. Systemic inflammation and disease progression in Alzheimer disease. Neurology. 2009;73:768-74.
67. Parra B, Slots J. Detection of human viruses in periodontal pockets using polymerase chain reaction. Oral Microbiol Immunol. 1996;11:289-93.
68. Iwai T. Periodontal bacteremia and various vascular diseases. J Periodontal Res. 2009;44:689-94.
69. Nakayama K. Porphyromonas gingivalis cell-induced hemagglutination and platelet aggregation. Periodontol. 2000 2010; 54:45-52.
70. Watts A, Crimmins EM, Gatz M. Inflammation as a potential mediator for the association between periodontal disease and Alzheimer's disease. Neuropsychiatr Dis Treat. 2008;4:865-76.
71. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE ε4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999;282:40-6.
72. Rainero I, Bo M, Ferrero M, Valfrè W, Vaula G, Pinessi L. Association between the interleukin-1alpha gene and Alzheimer's disease: a meta-analysis. Neurobiol Aging. 2004;25:1293-8.
73. Bretz WA, Weyant RJ, Corby PM, Ren D, Weissfeld L, Kritchevsky SB. Systemic inflammatory markers, periodontal diseases, and periodontal infections in an elderly population. J Am Geriatr Soc. 2005;53:1532-7.