Journal of Oral Biosciences 57 (2015) 139–142

Contents lists available at ScienceDirect

Journal of Oral Biosciences

journal homepage: www.elsevier.com/locate/job

Review

# The downward spiral of periodontitis and diabetes in Alzheimer's disease: Extending healthy life expectancy through oral health

Hiroshi Nakanishi*, Zhou Wu

*Department of Aging Science and Pharmacology, Faculty of Dental Sciences, Kyushu University, Fukuoka 812-8582, Japan*

ARTICLE INFO

*Article history:*
Received 31 March 2015
Received in revised form
28 April 2015
Accepted 28 April 2015
Available online 2 June 2015

*Keywords:*
Periodontitis
Alzheimer's disease
*Porphyromonas gingivalis*
Microglia
Oral brain science

ABSTRACT

*Background:* The Dominantly Inherited Alzheimer Network (DIAN) study revealed that the pathological changes associated with Alzheimer's disease (AD) begin decades before clinical symptoms occur. Therefore, attention has been focused on strategies to prevent AD progression. Evidence indicates that lifestyle related diseases, including diabetes and periodontitis, are risk factors for exacerbation of AD.
*Highlight:* Low-grade chronic systemic inflammatory signals associated with periodontitis and diabetes may activate primed or senescent microglia, which may provoke an exaggerated neuroinflammation. Furthermore, periodontitis and diabetes are often concurrent diagnoses, and the bidirectional relationship may include underlying contributors that amplify the chronic systemic inflammatory signals required for AD progression.
*Conclusion:* Effective management of periodontitis may contribute to prevention of AD, as periodontitis is both treatable and preventable. Therefore, brain health, which includes oral health as a contributing factor, is a promising strategy for achieving healthy life expectancy.


**Contents**



## 1. Introduction

The precise pathological brain changes occurring during Alzheimer's disease (AD) progression were recently described in the Dominantly Inherited Alzheimer Network (DIAN) study. Individuals with gene mutations associated with AD were followed over time in order to elucidate the disease process. The first changes in hippocampal volume are detected 15 years prior to the onset of symptoms. At five years prior to symptom onset, accumulations of amyloid β peptides (Aβ) in the brain peak and hippocampal

*Abbreviations:* AD, Alzheimer's disease; Dian, Dominantly Inherited Alzheimer Network; Aβ, amyloid β peptides; IRS-1, insulin receptor substrate 1; qRT-PCR, quantitative real-time reverse-transcription polymerase chain reaction; TNF-α, tumor necrosis factor-α; ROS, reactive oxygen species; CatB, cathepsin B; LPS, lipopolysacchide; APP, amyloid precursor protein; PPAR-γ, peroxisome proliferator-activated receptor-γ; CGA, chromogranin A; LPS, lipopolysaccharide

* Corresponding author. Tel.: +81 92 642 6413; fax: +81 92 642 6415.
*E-mail address:* nakan@dent.kyushu-u.ac.jp (H. Nakanishi).

http://dx.doi.org/10.1016/j.job.2015.05.002
1349-0079/

volume is severely reduced, after which the onset of mild cognitive impairment begins. At five years following symptom onset, intensive nursing care is often needed as a result of cognitive impairments. The DIAN study thus revealed that the pathological brain changes associated with AD begin decades before clinical symptoms appear.

An estimated 36 million people worldwide have AD or related dementias. Development of treatments that delay the onset of AD by five years is estimated to potentially reduce the number of AD patients by half. Recently, considerable attention has been focused on lifestyle related diseases, including diabetes [1] and periodontitis [2–5], as exacerbating factors for AD. Periodontitis is also a risk factor for diabetes, and several recent clinical studies have demonstrated that periodontal treatment using antibiotics has beneficial effects on glycemic control for patients with type 2 diabetes [6]. There is strong evidence that periodontitis is both treatable and preventable. Therefore, effective management of periodontitis is a potential alternative approach to preventing and ameliorating AD.

## 2. Brain insulin resistance in AD

Several recent clinical studies have indicated that type 2 diabetes mellitus, a pathological condition that is accompanied by peripheral insulin resistance, is a risk factor for cognitive dysfunction, including AD [7]. Consistent with metabolic changes resulting from peripheral insulin resistance, findings regarding brain insulin resistance in patients with AD contribute to understanding the pathology of AD. Talbot et al. demonstrated that insulin signaling is greatly reduced when phosphorylation of insulin receptor substrate 1 (IRS-1) occurs at several serine residues. This serine phosphorylation was previously confirmed as a feature of insulin resistance in AD brains without diabetes [8]. More recently, Hokama et al. examined gene expression profiles in postmortem human brains [9]. Three-way analyses of variance were performed on microarray data from the frontal cortex, temporal cortex, and hippocampus, with sex, presence/absence of AD, and vascular dementia as factors. Comparative analyses of gene expression changes in the brains of patients with AD and in a mouse model of AD were also performed. Relevant changes in gene expression identified by the microarray analyses were validated by quantitative real-time reverse-transcription polymerase chain reaction (qRT-PCR) and western blotting. AD brains had the most significant alterations in gene expression profiles in hippocampal tissue. Additionally, the expression of genes involved in non-insulin dependent diabetes mellitus and obesity was significantly altered in both the patient AD brains and the AD mouse model, as was that of genes associated with psychiatric disorders and AD. However, altered gene expression profiles in the AD brains were independent of peripheral diabetes mellitus related abnormalities. These results indicate that altered gene expression related to diabetes mellitus in AD brains is the result of AD pathology, which may therefore be exacerbated by peripheral insulin resistance and/or diabetes mellitus.

## 3. Clinical evidence for periodontitis as a risk factor for AD

The etiological hypothesis suggests that viruses and bacteria and/or their virulence factors access the brain and thereby contribute to the pathogenesis of AD. *Porphyromonas gingivalis* (*P. gingivalis*) and *Treponema denticola* are included in the red complex of risk factors due to their association with severe forms of periodontitis. These bacteria are invasive and virulent, inducing gingival inflammation that leads to connective tissue degradation and alveolar bone resorption around the teeth. Once the junctional epithelium that links the gingiva to the tooth enamel transforms to pocket epithelium, pathogenic bacteria induce bacteremia and initiate systemic inflammation by infiltrating the local blood vessels. Two studies using human brain tissue explored the impact of periodontal infection on AD [10,11]. These studies examined AD brain tissue specimens using molecular profiling methodologies to identify seven *Treponema* species [10] as well as the immunogenic endotoxin, lipopolysaccharide (LPS), from *P. gingivalis* [11]. In addition to oral pathogens, viruses such as herpes simplex virus Type 1 [12] and diverse bacteria, including *Chlamydia pneumonia* [13] and *Borrelia burgdorferi* [14], are found in the brains of patients with AD.

## 4. Possible link between periodontitis and AD: evidence from basic science studies

Recently, Matsushita et al. investigated whether *P. gingivalis*-evoked periodontitis impacts the pathological features of AD, using a transgenic mouse model [personal communication]. Cognitive functions were significantly impaired in J20 mice inoculated with *P. gingivalis* compared to control mice. Additionally, the levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ were higher in the brains of the inoculated J20 mice than in the brains of controls, and Aβ deposition in the hippocampus and cortex was also significantly greater in the inoculated J20 mice. Furthermore, the brain levels of pro-inflammatory cytokines, including interleukin 1β (IL-1β) and tumor necrosis factor-α (TNF-α), were higher in the inoculated mice than in the control mice. These results suggest that *P. gingivalis*-evoked periodontitis may exacerbate brain amyloid deposition and trigger brain inflammation, leading to further cognitive impairment.

## 5. Systemic inflammation and microglial priming

Perry et al. used a mouse model of prion disease to establish the concept of microglial priming [15,16]. Primed microglia exhibit an exaggerated response to even low-grade chronic systemic inflammation and produce exaggerated neuroinflammation. Systemic bacterial infection with *Salmonella typhimurium* stimulates microglia to secrete pro-inflammatory cytokines and express surface activation markers for several weeks [17]. Endothelial cells lining the blood–brain barrier also responded to systemic alarms by expressing adhesion molecules. Systemic infection leads to prolonged cytokine synthesis in the brain, as well as priming of brain innate immune cells to a subsequent focal inflammatory challenge in the brain parenchyma. Therefore, primed microglia contribute to the increased clinical symptoms experienced by patients with AD who also exhibit systemic inflammation and/or infection [18].

Microglia are also primed during healthy brain aging, so we refer to these microglia as senescent type microglia, which are distinct from primed microglia. Microglia isolated from the brains of aged, but not young, mice release interleukin-1β (IL-1β) in response to Aβ, indicating that senescence is an important contributor to AD [19]. Furthermore, systemic inflammation promotes microglia senescence, thereby increasing neuroinflammation in middle-aged, but not young, rats [20]. These changes are associated with deficits in hippocampal long-term potentiation, which is the cellular basis for learning and memory [21]. Therefore, it is necessary to elucidate the molecular mechanisms of microglial priming.

In the aging brain, electron transfer is impaired in some mitochondrial complexes, shifting the intracellular redox balance towards a more oxidized state. It is unknown whether this impairment also occurs in aged microglia, although it is likely that alterations in