How Do Periodontal Infections Affect the Onset and Progression of Alzheimer's Disease?

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Abstract: Chronic infection can cause slow progressive dementia, cortical atrophy and amyloid deposition in the atrophic form of general paresis. Due to the fact that specific bacterial ligands can increase the expression of proinflammatory molecules that can activate innate and adaptive immune systems, inflammation may play a significant role in the pathogenesis of Alzheimer's disease (AD). Furthermore, there is a significant association between AD and various types of spirochete. Periodontitis is a prevalent and persistent peripheral infection that is associated with gram-negative anaerobic bacteria and is capable of showing localized and systemic infections in the host. Periodontal disease related pathogens and their inflammatory products contribute to systemic inflammation and the pathogenesis of AD. In this mini-review, we propose a hypothetical link between periodontitis, type 2 diabetes and AD. We also present the possible mechanistic links between periodontitis-related inflammation, type 2 diabetes and AD. Since this condition is treatable, periodontitis may be a readily-modifiable risk factor for AD.

Keywords: Periodontal disease, Alzheimer's disease, inflammation, dementia.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that leads to amnesia, cognitive impairment and senile dementia. AD affects personal independence, relationships and the ability to express oneself comprehensibly. The disease is a devastating and fatal condition that results in a significant burden for the individual and society [1]. For these reasons, many researchers have investigated potential treatments for AD by focusing on various risk factors and pathological theories. For the prevention and management of this chronic disease, the identification of modifiable risk factors and preventive strategies is important.

Globally, an estimated 35.6 million people live with dementia [2]. The number of people with dementia is expected to double (65.7 million) by 2030 and by 2050, the number is expected to more than triple to 115.4 million [2]. Dementia affects people in all countries, but more than half (58%) of the population with dementia lives in low- and middle-income countries [2]. The most common cause of dementia is AD [3].

Periodontal disease (PD) is an inflammatory process that involves a progressive, episodic loss of the periodontal attachment apparatus. In susceptible patients, PD ultimately results in tooth loss. In individuals younger than 35 years old, the prevalence of moderate and severe PD is less than 1%, and an increasing prevalence is reported in older age groups [4]. In the USA alone, 25% of the population that is 75 years old and older suffers from PD (moderate PD: 18%; severe PD: 7%) [4]. A higher prevalence of PD is reported in the male population, and men are more likely than women to be at risk for PD [5]. PD is also implicated as being one of the primary complications in type 2 diabetes mellitus (T2DM) [6] and is hypothesized to predispose patients to AD [7].

In the majority of cases, the cause of AD is unknown. Most experts agree that AD is just like other common, chronic conditions that are likely to develop as a result of multiple factors rather than because of a single cause. AD is pathologically and genetically linked to T2DM [8, 9], although PD is only pathologically linked to T2DM [10]. Many questions remain about whether PD or cognitive impairment came first.

PDs are recognized as infectious processes that require the presence of bacteria and a host response. Risk factors in conjunction with bacteria and the host response can affect the severity of AD, patterns of destruction and responses to therapy. In the past decade, many studies have changed the approach to studying periodontal infection and the relationship between general health and PD. In this paper, we reviewed various published articles on PD as a potentially modifiable risk factor for AD.

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PATHOLOGY OF PD

The dental plaque biofilm is the most potent cause of direct and indirect periodontal tissue damage [11]. However, the majority of periodontal tissue injury is attributed to indirect mechanisms that are initiated by dental plaque, such as aggravated inflammatory host tissue response. Multiple complex interactions occur between the host defense cells and the periodontal tissues.

The inflammatory response in PD includes the activation of leucocytes, neutrophils, T-lymphocytes and plasma cells [12]. The inflammatory response also includes the release of antibodies, lipopolysaccharides (LPSs) and chemical inflammatory mediators, such as cytokines, chemokines and C-reactive proteins. LPSs are present in the gram-negative bacterial cell walls and act as powerful stimulants for complex host responses. The initial surge of neutrophils at the site is followed by the release of cytokines by neutrophils and macrophages. The released chemical mediators include tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and prostaglandins (PGs). The inflammatory process includes the stimulation of fibroblasts by IL-1 and the secretion of matrix metalloproteinases (MMPs) by polymorphonuclear neutrophils. While MMPs are responsible for increased collagen breakdown, TNF-α is primarily responsible for increased osteoclast activity that results in bone resorption. MMPs can also activate cytokines and chemokines, which can exacerbate the destructive process. The production of collagen is inhibited by reduced fibroblast activity in response to TNF-α [13-15] (Fig. **1**).

Lymphocytes release antibodies as protective mechanisms. However, lymphocytes also activate the osteoclasts that result in bone loss [16]. T-lymphocytes secrete the receptor activator nuclear factor kappa-B ligand (RANKL), which is involved in osteoclast activity and leads to bone resorption. The destructive inflammatory mediators are inhibited by the presence of osteoprotegerin and the secreted tissue inhibitors of metalloproteinases (TIMPs) [14, 17, 18].

The level of periodontal destruction depends on the balance between destructive and protective inflammatory mediators. While periodontal bacteria are required for infective PD, an individual's response determines the disease progression. *In vitro*, an individual's response can be affected by genetic signaling pathways that influence the expression of inflammatory mediators in response to bacterial LPS [13-18].

During periodontitis, pathogens such as *Porphyromonas gingivalis* (*P. gingivalis*), *Tannerella forsythia* and *Treponema denticola (T. denticola)* are associated with the formation of biofilm [19]. In the innate immune system, a family of pattern-recognition receptors named toll-like receptors (TLRs) recognizes the pathogen-associated molecular patterns of these gram-negative bacteria [20, 21]. These receptors are predominantly expressed on the surface of neutrophils, monocytes and dendritic cells, and they orchestrate a rapid innate immune response against invading pathogens [20-22]. The activation of TLRs (except for TLR3) induces the interaction between the IL-1 receptor domain-containing protein and the adaptor protein myeloid differentiation primary response gene (MyD88). MyD88 recruits a protein kinase, such as the IL-1 receptor-associated kinase, to induce the mitogen-activated protein kinase kinase kinase (MAP3K). In turn, MAP3K activates the mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinases (JNKs), p38 and the transcription factor nuclear factor-kappa B (NF-κB) [23]. The induction of NF-κB activity contributes to the secretion of various key inflammatory mediators of chronic inflammatory conditions, including TNFα, interleukin-1b (IL-1b) and prostaglandin E2 (PGE2) [24, 25]. In patients with chronic periodontitis, enhanced levels of TNFα have been found in the serum and gingival crevicular fluid [26, 27] (Fig. **1**).

In addition to the beneficial role of TLRs in the host immune response, the stimulation of TLR signalings, primarily *via* TLR2 and TLR4, may contribute to the development of a number of diseases that are promoted by chronic inflammatory processes. For example, TLR2 has

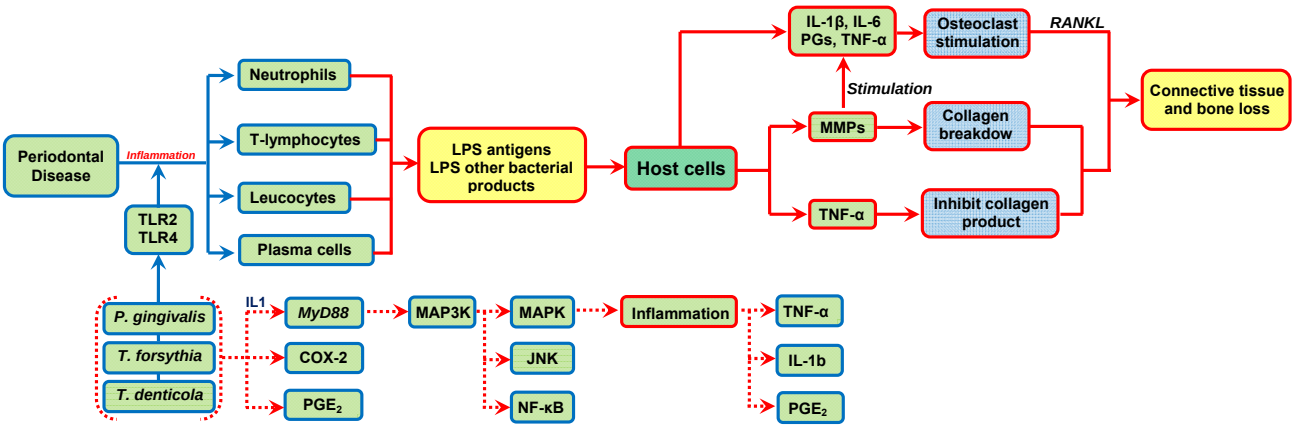

Fig. (1). Pathogenesis of periodontal diseases (PDs). LPS: lipopolysaccharide; IL: interleukin; PGs: prostaglandins; TNF: tumor necrosis factor; MMPs: metalloproteinases; RANKL: receptor activator of nuclear factor kappa-B ligand; MyD88: myeloid differentiation primary response gene: COX-2: cyclooxygenase 2; PGE2: prostaglandins E2; MAP3K: mitogen-activated protein kinase kinase kinase; JNK: c-Jun N-terminal kinases; NF-κB: nuclear factor-kappa B; TLR: toll-like receptors.

been implicated in systemic lupus erythematosus, diabetes and AD [28, 29]. Compared to periodontally healthy controls, studies have reported elevated levels of TLR2 and TLR4 in the gingival tissues of patients with chronic periodontitis [30]. In patients with PD, Lappin *et al*. [31] demonstrated that the levels of TLR2 and TLR4 agonists, Pam3Cys-Ser-(Lys)4 (Pam3CSK4).” and LPS are elevated in the saliva. In addition, gingival fibroblasts, which are the major cell type in the periodontal connective tissue, express both TLR2 and TLR4 [32, 33]. Gutierrez-Venegas *et al*. [34] demonstrated that gingival fibroblasts that are treated with the specific TLR2 ligand LPS (from the periodontitis-associated bacteria *P. gingivalis*) promoted the expression of cyclooxygenase-2 (COX-2) and PGE2 synthesis. While TLR2 is expressed in the gingival tissues of patients with periodontitis and the expression of the receptor increases with chronic inflammation [35], the signaling pathways that are involved in the induction of TLR2 remain unclear. Further investigation is needed to elucidate the exact role of TLR2 gene expression in PD inflammation.

LINKAGE BETWEEN PD AND T2DM (FIG. 2)

PD has been coined as the “sixth complication” of diabetes [6]. T2DM is a genetically and environmentally based chronic metabolic and vascular syndrome that is caused by insulin deficiency and alterations in lipids, carbohydrates and proteins metabolisms [10]. Hyperglycemia is the primary consequence of defects in the secretion and/or action of insulin. Alterations in insulin synthesis can affect various organs, especially including the kidneys, eyes, nerves, blood vessels and immune systems [10]. Furthermore, chronic hyperglycemia is associated with an inflammatory response that is linked to complications that are observed in diabetes.

In patients with PD, oral pathogens and their products can gain access to the systemic circulation, which may elicit an immune response that can disrupt the body’s normal homeostasis. Combined with the presence of infection and an exaggerated host response, the accumulation of advanced glycation end products (AGEs) that occurs as a result of a chronic hyperglycemic state may explain the clinical outcomes that are observed in diabetic patients with PD [10]. Since the effective control of periodontal infection in diabetic patients reduces the level of AGEs in the serum [10], proper glycemic control is an important factor that should not be overlooked.

Bacterial products, such as endotoxin or LPS, also propagate an inflammatory response in the host through the TLRs, which induces an inflammatory cascade [36]. These receptors play an important role in the innate immune response, particularly in the initial interaction between the infecting microorganisms, such as *P. gingivalis* and phagocytic cells of the monocyte lineage [37]. Genetic and biochemical studies have shown that the toll protein family members play a critical role in the immediate response to infection [38, 39]. While LPS monocyte interactions provide one of the best-studied models of innate immunity using gram-negative bacteria and the bacterial endotoxin, the mechanisms behind PD and the regulation of TLR protein expressions are not well understood. Collectively, these

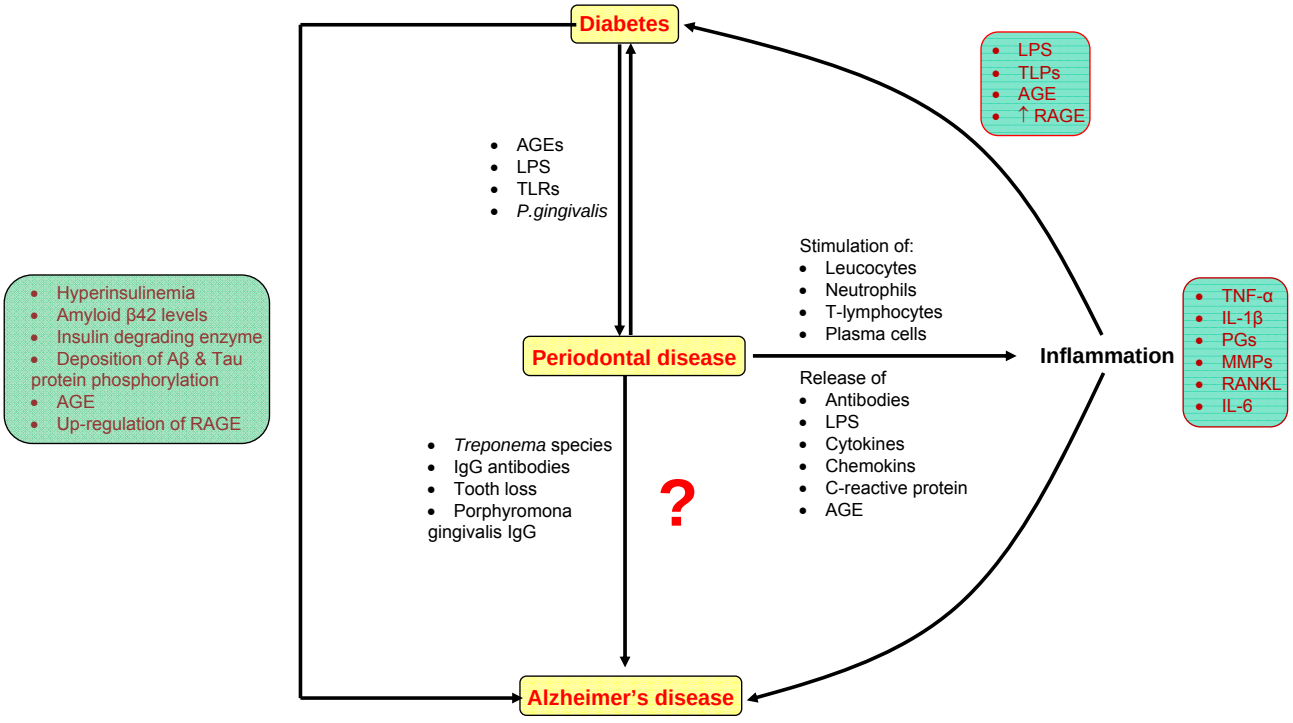

Fig. (2). Schematics of the linkages among periodontal disease; Alzheimer’s disease and type 2 diabetes mellitus. LPS: lipopolysaccharide; IL: interleukin; PGs: prostaglandins; TNF: tumor necrosis factor; MMPs: metalloproteinases; RANKL: receptor activator of nuclear factor kappa-B ligand; TLR: toll-like receptors; AGE: advanced glycation end products; TLPs: toll-like receptor proteins; RAGE: receptor of advanced glycation end products.

studies have provided insight into the molecular mechanisms that support the observed epidemiological associations between PD and diabetes.

LINKAGE BETWEEN T2DM AND AD (FIG. 2)

In addition to having neuroprotective effects, a recent study suggests that insulin plays primary roles in reducing blood sugar levels and acting as a growth factor in neuronal stem cell activation [40]. Independent of cerebrovascular disease, hyperinsulinemia is a plausible risk factor for late-onset Alzheimer's disease (LOAD), as insulin can cross the blood-brain barrier [41]. Moreover, peripheral insulin infusion may affect amyloid β42 (Aβ42) levels in cerebrospinal fluid in the elderly [42]. Aβ42 is a marker for amyloid β (Aβ) clearance in the brain, and Aβ42 is an indirect marker for the risk of LOAD. Furthermore, the number of insulin receptors in the brain, especially in the structures in the hippocampus and entorhinal cortex that are affected early during LOAD [43, 44] can be increased. The insulin-degrading enzyme (IDE) also plays a role in the clearance of Aβ in the brain, as both insulin and Aβ compete for IDE [45]. In the pathogenesis of LOAD, the deposition of key markers (Aβ and tau protein phosphorylation) can be increased by the presence of insulin in brain [41].

The pathways related to insulin in the periphery with Aβ clearance in the brain are multiple and complex. Craft el al. reviewed the literature on how peripheral hyperinsulinemia affects amyloid beta clearance in the brain [8]. Due to saturation above physiologic levels, one potential pathway is that peripheral hyperinsulinemia downregulates insulin uptake in the blood brain barrier [18]. Peripheral hyperinsulinemia may result in the reduction of 1) insulin levels in the brain and the downregulation of IDE expression [46] and 2) IDE-mediated amyloid clearance [45]. This complex observation supports the seemingly paradoxical use of the insulin sensitizer rosiglitazone [9, 47] and intranasal insulin [48] in the treatment of LOAD.

Elevated glucose concentration promotes the accrual of AGEs, AGEs are closely linked with both glycemia and diabetes. In hyperglycemic environments, diabetic animal and human tissues contain increased AGE levels that promote the up-regulation of the AGE receptor (RAGE) [49]. AGE is associated with the traditional microvascular complications of T2DM [50]. Increased expressions of RAGE are also observed in LOAD [51], and the expression of RAGE is enhanced in blood vessels that are adjacent to Aβ deposits in the LOAD brain [52].

LINKAGE BETWEEN PD AND AD (FIG. 2)

Due to the interaction between periodontopathic bacteria and the host response, a significant number of inflammatory molecules (IL-1β, IL-6 and TNF-α) are produced during brain inflammation [53]. In the brains of AD patients compared to non-AD subjects, studies have reported a relatively higher spirochetes burden, including *Treponema* species (periodontal pathogens) [54, 55]. Thus, inflammatory molecules and the aforementioned pathogens may play a role in the brain inflammation that characterizes and affects the expression of AD [56]. Moreover, clinical studies have reported that tooth loss is a significant risk factor for AD and/or dementia [57, 58]. While tooth loss may have several causes [59, 60], PD is one of the major causative factors for loss of tooth in adults. Even after extensive adjustments for confounders, the Third National Health and Nutrition Examination Survey (NHANES III) reported that gingival bleeding, loss of periodontal attachment and serum *P. gingivalis* IgG, all of which can indicate PD, were significantly associated with lower cognitive function [61, 62].

Inflammation is one of the key features of AD and provides the foundation for the hypothesis that inflammatory and infectious conditions may be risk factors for AD. PD can contribute to the expression of AD *via* several mechanisms [56]. Peripheral inflammation and infections play important roles in the pathogenesis of AD [63-65] and affect oral bacteria [66-69]. Furthermore, the systemic dissemination of bacterial species from local infections may affect AD [68]. During various surgical and non-surgical procedures, oral bacteria from the periodontal species can gain access to systemic circulation and colonize distant anatomical sites, which can lead to pathologies such as endocarditis and brain and lung abscesses [70]. While they were absent in healthy controls, spirochetes have been found in the blood, cerebrospinal fluid and brain samples of AD patients [54, 71], which further supports the colonization occurring *via* systemic spread. Using molecular techniques with *Treponema* species, including *T. denticola*, a pathogenic periodontal bacterium was detected in the brains of AD patients [55]. *T. denticola* belongs to the same class as *T. pallidum* and is known to induce pathologic conditions that are comparable with the pathology found in AD [68].

Among periodontal patients, a significant number of IgG antibodies to *T. denticola* have been reported [72]. However, no study has investigated the levels of IgG antibodies among AD patients, and there are no clinical studies that directly link PD and AD. Some studies have used antibodies to periodontal bacteria to discover associations between PDs and other systemic diseases [73-75]. The elevated antibodies *Actinobacillus actinomycetemcomitans* and *P. gingivalis* are better associated with cardiovascular disease than with clinical PD measures [76] which suggest that antibodies to periodontopathic species may provide an index of exposure for investigations of the relationship between PD and systemic diseases.

The biological reason for an association between antibody levels to periodontal bacteria and AD is unknown. AD subjects have been shown to have poor oral hygiene [77], which would suggest higher antibody levels and increased bacterial colonization. Over 500 bacterial species can colonize the supragingival and subgingival environments (the areas above and below the gingival margin, respectively) around the teeth [11]. The presence of pathogenic species has also been reported in healthy subjects. Recent studies suggest that the host inflammatory response may be more important in bacterial biofilm formation than was originally thought [78]. Furthermore, recent studies on the association between measures of periodontal infections and cognitive functions in the normal population have suggested that the association may be established even before the onset of AD [61, 62].

One study has indicated that subjects with TNF-α and IgG antibodies against periodontal pathogens have higher risk for AD, which suggests that TNF-α may not be related to the number of positive antibody responses [79]. In the presence of systemic inflammation, periodontal infection may lead to an increased risk for systemic diseases. Increased age and the presence of teeth may influence antibody levels [80], and the elderly may also have a reduced antibody response [81, 82]. Since AD patients tend to be older than non-AD patients, the level of antibody response in AD may actually be underestimated. Furthermore, the antibody response reflects the host immune function, so antibody titres to periodontal bacteria may compliment plasma TNF-α levels and improve the clinical diagnosis of AD. In this way, AD patients can be differentiated from cognitively normal subjects.

CONCLUSION

Patients with no cognitive impairment who have elevated antibodies to PD bacteria may have an increased risk of AD onset and/or progression. At the same time, the incidence and severity of T2DM from PD may aggravate cognitive impairment. Inflammatory chemical mediators that exist in the presence of bacterial products and alterations in the inflammatory gene expression can contribute to AD. The goals of this study were to understand the association between chronic oral periodontal infection and AD and to determine whether the chronic oral infection could contribute to the risk of AD expression. The current findings suggest an increased risk; however, additional cohort studies that profile oral clinical presentation with systemic response and AD are needed, and prospective studies can evaluate any cause-and-effect association. The hope is that future studies will elucidate the importance of maintaining oral health as a fundamental part of healthy aging and to lower the risk of these types of neurological changes. Global attention and action are needed to support this emerging field of research. In the future, dementia may be prevented by combining antibiotic, antiviral and anti-inflammatory therapies.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
Aβ42	=	Amyloid β42
IDE	=	Insulin-degrading enzyme
LOAD	=	Late-onset AD
LPS	=	Lipopolysaccharides
MMPs	=	Matrix metalloproteinases
PD	=	Periodontal disease
TLRs	=	Toll-like receptors
TNF-α	=	Tumor necrosis factor-alpha
T2DM	=	Type 2 diabetes mellitus

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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