**Tooth Loss and Alzheimer's Disease**

Tetsuya Goto, DDS, PhD[1], W. Keung Leung, MDS, PhD[2]

A concise and informative title: Tooth Loss and Alzheimer's Disease

[1]Division of Oral Anatomy and Cell Biology

Graduate School of Medical and Dental Sciences

Kagoshima University

Kagoshima 890-8544, Japan

Tel: +81-99-275-6100

E-mail: tgoto@dent.kagoshima-u.ac.jp

OCID: 0000-0002-9935-8971 (T Goto)

[2] Periodontology, Faculty of Dentistry,

The University of Hong Kong,

Hong Kong SAR, China

Tel: +852-2859-0417

E-mail: ewkleung@hku.hk

OCID: 0000-0003-1979-910X (WK Leung)

Corresponding author:

Tetsuya Goto

E-mail: tgoto@dent.kagoshima-u.ac.jp

Tel: +81-99-275-6100

Fax: ;81-99-275-6108

**Abstract**

**Purpose of Review**: Alzheimer's disease (AD) is a major subtype of dementia. Recent cohort studies have demonstrated that loss of masticatory function, periodontitis, and/or tooth loss are risk factors for AD. The present review provides an overview of the existing literature as well as recent evidence regarding the relationship between tooth loss and the onset of AD.

**Recent findings**: In the dental field, tooth loss is one of the most relevant factors related to the prevalence of AD. This is important in a progressively elderly population because tooth loss is associated with the risk of mild cognitive impairment (MCI) developing into dementia due to a cascade of neurodegeneration caused by damage to periodontal tissues via the trigeminal nerve, locus coeruleus (LC), and hippocampus. Additionally, periodontal disease and/or the loss of masticatory function are likely to exacerbate factors associated with AD.

**Summary:** Tooth loss in the elderly may cause neurodegeneration and act as a trigger for the progression from MCI to dementia. Moreover, neurodegeneration due to tooth loss is thought to exacerbate the accumulation of AD-specific amyloid-β and phosphorylated tau proteins, which worsen the pathological condition of AD. Although further evidence is needed, novel strategies for avoiding the progression to AD due to tooth loss in the elderly are required.

**Keywords**: Tooth loss, Alzheimer's disease, periodontitis, neurodegeneration

## Introduction

Mild cognitive impairment (MCI) or dementia is a growing health problem in the aging global population. According to Alzheimer's Disease International, the regional estimates of dementia prevalence in people ≥60 years old range from 4.6% in Central Europe to 8.7% in North Africa and the Middle East, while all other global regions are 5.6 - 7.6%, and around 58% of the affected were in low- and middle-income countries [1]. The strongest evidence for possible causal associations with dementia was for low education in early life, hypertension in midlife, and smoking and diabetes across the life course [2].

Alzheimer's disease (AD) is the most common cause of dementia in older adults and is one of the most important medical issues in countries where population aging appears inevitable. In 2013 the Group of Eight declared that dementia is a global priority issue and its treatment should be available by 2025 [3]. Other dementias include Lewy body dementia, frontotemporal disorders, and vascular dementia. It is common for people to have mixed dementia —a combination of two or more types of dementia. According to National Institute on Aging (NIA), dementia is a brain disorder that affects communication and performance of daily activities and AD is a form of dementia that specifically affects parts of the brain that control thought, memory and language.

AD is a neurodegenerative disorder of brain neurons characterized by formation of plaques and tangles with yet ill-defined cause and no effective treatment available [4]. Plaques were formed by β- other than α-secretase teaming up with γ-secretase in digestion/recycle of amyloid precursor protein (APP) giving rise to insoluble amyloid β (Aβ) peptides which form clumps or the beta amyloid plaque in the brain extracellular milieu. Increased amyloid plaque formation could also resulted from APP precursor protein gene mutation or associated with less effective Aβ clearance related to apolipoprotein E ε4. The

amyloid plaque can disrupt signaling between neurons, trigger immune response hence inflammation promoting further neural damages. Beta amyloid plaque if deposited around brain blood vessels can induce cerebral amyloid angiopathy hence hemorrhage and brain bleeds. Tangles were form inside the neurons where amyloid plaque somehow activated an army of kinases which phosphorylated the microtubule-associated protein tau leading to formation of neurofibrillary tangles. The affected microtubule structure was disrupted and therefore impairing many cellular processes which eventually leads to apoptosis of the affected cell. Hippocampal neurofibrillary tangles are related to dementia severity within elderly patients, and amyloid plaque deposition is related to the extent of AD-related neuropathological lesion [5].

Taking the above together, AD indeed, could qualify as a member of complex human diseases. Apparently, a great deal of researches provided detailed information on the pathological events related to molecules as mentioned above in association with different stages of dementia [6, 7], the cause of AD, however, remained not well appreciated, and effective treatment remained lacking [4]. Since there is deficiency in effective AD treatments strategy, the targets of many AD studies now focus on the prevention of MCI [3].

Until the early 2000s, the relationship between dementia and dentistry primarily focused on oral hygiene and behavioral management and communication for dental care [8]. According to data from this time period, the prevalence of AD was 10–15% in people older than 65 years of age and 20% in people older than 80 years of age [8]. Of the diseases that are primarily associated with the elderly, heart disease, malignant neoplasm, and cerebrovascular disease represented the top causes of mortality in elderly people in the early 2000s [9]. The prevalence of dementia in 2000 was not as high as it is now; thus, dentists were more interested in managing the treatment of dementia patients who visited dental clinics. Review

articles from that time period introduced treatments for people with dementia in special facilities for elderly people, suggested management strategies for patients with dementia in dental offices, and provided options for the performance of oral care in this population [10-12].

Beginning in the early 2000s, very interesting findings regarding dental care in patients with dementia were reported. A study in twins that conducted co-twin control analyses found that only a history of tooth loss before 35 years of age was a significant risk factor for AD, whereas a low education level contributed to the risk of total dementia, and a lack of physical exercise was associated with non-Alzheimer's dementias [13]. These authors emphasized that education and physical exercise exhibited stronger associations for other dementias than for AD and that tooth loss was a significant risk factor only for AD and not for other types of dementia. Because the subjects in that study were younger than 35 years of age, tooth loss was not due to aging but rather a lack of oral care. These findings are interesting because they established a link between tooth loss and dementia in a cohort of twins. Since that time, many cohort studies have been conducted, and oral environmental factors related to the onset of dementia have gradually been identified. For example, periodontal diseases and number of residual teeth are strongly correlated with the onset of dementia.

**Cohort studies of the effects of tooth loss on dementia**

Many cohort studies investigating risk factors related to the progression of AD have revealed an association between oral health and dementia risk in elderly people. Tooth loss, cavities, and periodontal disease appear to be risk factors that contribute to the progression of cognitive dysfunction [14], and poor oral health leads to tooth loss at the end stages of various

oral diseases, including cavities and periodontal disease. Several large clinical surveys conducted in Sweden [15], Italy [16], Germany [17], China [18], and Japan [19, 20] have also revealed a relationship between tooth loss and dementia risk. An initial report proposed that dementia may be associated with the discontinuation of regular dental checkups which, in turn, results in poor oral health [15,16] (Table 1). Later reports focused on the relationships between Mini-Mental State Examination (MMSE) scores and the number of remaining teeth [17], the progression of cognitive dysfunction from MCI to dementia and the number of lost teeth [18], and the risk of all-cause dementia and the number of remaining teeth [20]. This change in viewpoint indicates that tooth loss is not due to a lack of oral health care associated with the progression of dementia, although this may be partially correct, but rather that tooth loss is directly associated with the progression of dementia.

Subsequently, the issue of how tooth loss interacts with dementia became important. Currently, the effects of tooth loss on the progression of dementia are thought to be due to chronic inflammation induced by reduced masticatory forces [21, 22], periodontitis [23, 24], and neurodegeneration in the central nervous system [25].

**Mastication and dementia**

The relationship between eating/swallowing and dementia in relation to tooth loss is an interesting topic for dentistry. There are two perspectives: 1) how dementia influences mastication, and 2) how a loss of masticatory function affects the progression of dementia. To assess how dementia influences mastication, Miura et al. [26] compared the masticatory abilities of aged women suffering from dementia with those of healthy women and found that the cognitively impaired population exhibited inferior scores for maximum bite force, occlusal contact area, and mastication. Furthermore, a major issue for elderly individuals with

impaired cognitive functions is difficulty in retaining and controlling dental health care [27, 28].

Many studies, including animal studies, have been performed to evaluate how a loss of masticatory function affects dementia. Experimental studies have shown that removing the molars in mice leads to impairments in learning and spatial memory [29-31]. Onozuka et al. [32] suggested that disruption of the hypothalamic-pituitary-adrenal axis induces elevated plasma corticosterone levels and Ono et al. [33] proposed that impaired mastication due to tooth loss induces chronic stress in animals. Several human case studies have focused on the effects of mastication on cerebral blood flow (CBF), based on findings that mastication increases CBF in young adults [34-36]. It has been shown that both hippocampal activity and performance on a memory task increase in aged participants after chewing [37]. Additionally, mastication-induced enhancement of prefrontal cortical activity may be associated with better performance because over-recruitment of brain areas was observed in older adults with better cognition [38]. Although these findings suggest that tooth loss can be expected to reduce CBF in the elderly population, no strong evidence has been presented to show that decreased CBF is due to tooth loss. Currently, no direct relationships between CBF and changes in occlusion or neurodegeneration as seen in AD have been observed. It is possible that the deterioration of occlusion associated with tooth loss is indirectly involved in the progression of dementia but not directly related to the onset of dementia.

**Periodontitis and dementia**

Periodontal disease is the most likely oral health factor to have a relationship with the onset of AD due to its association with anaerobic bacteria and viruses. A recent review reported that approximately 10% of the global population suffers from severe forms of

periodontal disease based on a score of 4 on the Community Periodontal Index of Treatment Needs (CPITN) [39]. Periodontal disease can result in tooth loss if untreated. Therefore, it is important to evaluate the relationship between periodontal disease and dementia, particularly the roles played by pathogenic bacteria, bacterial toxins, and chronic inflammation. The prevalence of severe periodontitis increases with age, but peaks at age 40 and remains stable thereafter [39]. A human study conducted by Kaye et al. [40] assessed chronic periodontitis by probing depths and attachment loss and found that this disease is associated with low cognitive scores. Other studies have found no association between the severity of periodontal disease and dementia [41-46]. Thus, the relationship between periodontal disease and dementia remains unclear, but this may be due to differences in the survey methods used in different countries.

It is also important to consider the systemic effects of periodontal disease-related bacteria in the blood circulation when assessing dementia. Strong epidemiological evidence indicates that periodontitis imparts an increased risk for future atherosclerotic cardiovascular disease [47]. The effects of periodontitis-related bacteria on systemic disease may manifest when an infection spreads from the oral cavity to a distant site that is then colonized by those specific bacteria, and subsequently, systemic inflammation arises due to an inflammatory immune response caused by the oral infection [48]. Pool et al. [49] investigated the relationship between dementia and periodontal bacteria and found that the major periodontal bacteria species is *Porphyromonas gingivalis* (Pg), and that its lipopolysaccharide (PgLPS) has been detected in the brains of AD patients; this finding has had a strong impact in this area of research. Subsequent studies reported that PgLPS induces activation of the leptomeninges/choroid plexus, which is formed at the blood-cerebrospinal fluid barrier (BCSFB), and results in microglia-mediated neuroinflammation [50, 51]. Recently, Dominy

et al. [52] demonstrated that an inhibitor targeting small molecule gingipain may be valuable for treating Pg brain colonization and neurodegeneration in AD. These authors reported that oral Pg infections in mice result in brain colonization and the increased production of a component of amyloid plaques. Furthermore, gingipains are neurotoxic both in vivo and in vitro and exert detrimental effects on tau. Taken together, these studies indicate that periodontal disease-related bacteria, particularly Pg, influence the progression of dementia.

However, there still remains two unresolved problems concerning the relationship of AD and periodontal disease. One is that the periodontal disease becomes severe at middle age, but dementia progresses occur at elder age, and the other is that initial stage of dementia starts from a specific place such as the hippocampus, not the entire brain. Thus, it would be possible that periodontal disease-related chronic inflammation exacerbates the AD process.

**Novel findings on the effects of tooth loss**

Although many cohort studies have observed a relationship between the prevalence of AD and tooth loss or the number of residual teeth, no neuropathological evidence supporting this relationship has been presented to date. Dementia, including AD, is essentially a neurodegenerative disease. The neuropathological findings of AD differ from those of other types of dementia; thus, the present review will mainly discuss AD-related neurodegeneration. It is generally accepted that the major pathological findings of AD include the formation of amyloid plaques via the deposition of Aβ and the formation of neurofibrillary tangles via phosphorylated tau. Sperling et al. [4] reported that the deposition of Aβ in the central nervous system begins at a young adult age, even as young as 30 years old, and then gradually reaches a plateau at approximately 60–70 years of age. Adults of this age are not yet associated with the stage of dementia but are associated with MCI or the

preclinical stage of dementia. Although Aβ can be considered a type of garbage that is emitted from nerves, it will be necessary to determine the original primary function of APP-containing Aβ. Because the current issue is the type of neurodegeneration that influences the progression from MCI to dementia, the influence of tooth loss in this regard will be discussed.

Initial AD-related neurodegeneration appears to begin in the nucleus basalis of Meynert, the entorhinal cortex, and the LC [53], after which it spreads to most of the brain, including the cerebral cortex, basal forebrain, amygdala, and hypothalamus [54]. During tooth extraction, the trigeminal nerve is differentiated, thus it is important to investigate which of three neural sites may be affected by neurodegeneration after tooth extraction. The most likely site is the trigeminal mesencephalic nucleus (Me5) because it is located adjacent to the dorsal side of the LC [55]. The nerve endings present in the periodontal ligament that are damaged during tooth extraction are nociceptive-free, mechanoreceptive, vascular nerve endings. In these types of nerve endings, Ruffini endings act as mechanoreceptors, and it is known that the somata of periodontal afferents are located in Me5 [56]. Because the neurodegeneration of Me5 neurons results in their loss [57], it can be expected that Me5 neurons affected during tooth extraction will die. Subsequently, it is likely that additional negative factors can affect LC neurons.

In preliminary experiments from our research group, the extraction of molars in mice resulted in the decrease of LC neurons as well as Me5 neurons. It is also known that tooth loss decreases hippocampal neurons [25] and that AD-related neurodegeneration cascades from Me5 neurons to the LC to the hippocampus, which could lead to the onset or progression of dementia. It is also possible that dental deafferentation may cause brain damage via altered cerebral circulation and dysfunction [58]. Despite the evidence presented in the above studies, it is necessary to conduct further histopathological and behavioral experiments in appropriate

AD mouse models to fully elucidate the relationship between tooth loss and AD. Actually, experiments using wild type mice or rat have not found clear data to indicate the effects of tooth loss on the progress of dementia [59, 60], and using different type of transgenic AD model mice negative effects of tooth loss were found [61]. To investigate the effect of tooth loss using an AD model mice, before tooth extraction it is necessary to clarify the predementia period of the AD model mice.

## Conclusions

According to previous cohort studies, the number of teeth may be a more important risk factor for AD than periodontal disease, which is closely related to the prevalence of dementia. Periodontal disease and masticatory disorders appear to exacerbate dementia rather than serve as causative factors, because the age of onset for dementia is relatively late. Additionally, the effects of tooth loss on the onset of dementia are due to masticatory disorders as well as the cascade of neurodegeneration due to tooth loss (Fig.1).

Because dementia is generally considered a neurodegenerative disorder, it is important to identify where neurodegeneration begins. If the cascade of neurodegeneration proposed in the present review is correct, then tooth extraction in the elderly population may be a trigger for the progression of dementia, especially in patients with MCI who are at a high risk for a shift to dementia. Therefore, to avoid tooth extraction, it will be necessary to focus on the prevention of periodontal disease and to consider preventive methods that do not promote dementia, even if tooth extraction is needed. Finally, it will be necessary to collect further evidence using appropriate animal models of AD and effective experimental protocols that can clarify the relationship between tooth loss and dementia.

**Compliance with Ethical Standards**

**Conflict of Interest** The author declares that he has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the author.

**References**

Papers of particular interest, published recently, have been highlighted as:

• Of importance


1. Ali GC, Guerchet MM, Wu Y-T, Prince MJ, Prina M. The global prevalence of dementia. World Alzheimer Report 2015 - The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International, 2015. 10-29.
2. Prince MJ, Albanese E, Guerchet MM, Prina M. Key message. World Alzheimer Report 2014 – An analysis of protective and modifiable factors. London: Alzheimer's Disease International, 2014. p5.

**3.** *Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. Lancet. 2016;388(10043):505-17. **This manuscript well summarized recent knowledge about Alzheimer's disease.**

4. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnosticguidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92.

**5.** Rapp MA, Schnaider-Beeri M, Purohit DP, Reichenberg A, McGurk SR, Haroutunian V, Harvey PD. Cortical neuritic plaques and hippocampal neurofibrillary tangles are related to dementia severity in elderly schizophrenia patients. Schizophr Res. 2010116(1):90-6.

6. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9(1):119-28.

7. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011; 70(11):960-9.

8. Kocaelli H, Yaltirik M, Yargic LI, Ozbas H. Alzheimer's disease and dental management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93(5):521-4.

9. Ghezzi EM, Ship JA. Systemic diseases and their treatments in the elderly:impact on oral health. J Public Health Dent. 2000;60(4):289-96.

10. Chalmers JM. Behavior management and communication strategies for dental professionals when caring for patients with dementia. Spec Care Dentist. 2000;20(4):147-54.

11. Chalmers J, Pearson A. Oral hygiene care for residents with dementia: a literature review. J Adv Nurs. 2005;52(4):410-9.

12. Rejnefelt I, Andersson P, Renvert S. Oral health status in individuals with dementia living in special facilities. Int J Dent Hyg. 2006;4(2):67-71.

13. Gatz M, Mortimer JA, Fratiglioni L, Johansson B, Berg S, Reynolds CA, Pedersen NL. Potentially modifiable risk factors for dementia in identical twins. Alzheimers Dement. 2006;2(2):110-7.

14. Delwel S, Binnekade TT, Perez RSGM, Hertogh CMPM, Scherder EJA, Lobbezoo F. Oral hygiene and oral health in older people with dementia: a comprehensive review with focus on oral soft tissues. Clin Oral Investig. 2018;22(1):93-108.

15. Fereshtehnejad SM, Garcia-Ptacek S, Religa D, Holmer J, Buhlin K, Eriksdotter M, Sandborgh-Englund G. Dental care utilization in patients with different types of dementia: A longitudinal nationwide study of 58,037 individuals. Alzheimers Dement. 2018;14(1):10-19.

16. D'Alessandro G, Costi T, Alkhamis N, Bagattoni S, Sadotti A, Piana G. Oral Health Status in Alzheimer's Disease Patients: A Descriptive Study in an Italian Population. J Contemp Dent Pract. 2018 May 1;19(5):483-489.

17. Grabe HJ, Schwahn C, Völzke H, Spitzer C, Freyberger HJ, John U, Mundt T, Biffar R, Kocher T. Tooth loss and cognitive impairment. J Clin Periodontol. 2009;36(7):550-7.

18. Luo J, Wu B, Zhao Q, Guo Q, Meng H, Yu L, Zheng L, Hong Z, Ding D. Association between tooth loss and cognitive function among 3063 Chinese older adults: a community-

based study. PLoS One. 2015;10(3): e0120986.

19. Okamoto N, Morikawa M, Okamoto K, Habu N, Hazaki K, Harano A, Iwamoto J, Tomioka K, Saeki K, Kurumatani N. Tooth loss is associated with mild memory impairment in the elderly: the Fujiwara-kyo study. Brain Res. 2010;1349:68-75.

20. *Takeuchi K, Ohara T, Furuta M, Takeshita T, Shibata Y, Hata J, Yoshida D, Yamashita Y, Ninomiya T. Tooth Loss and Risk of Dementia in the Community: the Hisayama Study. J Am Geriatr Soc. 2017;65(5):e95-e100. **This cohort study clearly shows the association of the number of remaining teeth and the risk of dementia.**

21. Weijenberg RA, Scherder EJ, Lobbezoo F. Mastication for the mind—the relationship between mastication and cognition in ageing and dementia. Neurosci Biobehav Rev. 2011;35(3):483-97.

22. Lexomboon D, Trulsson M, Wårdh I, Parker MG. Chewing ability and tooth loss: association with cognitive impairment in an elderly population study. J Am Geriatr Soc. 2012;60(10):1951-6.

23. Kamer AR, Craig RG, Dasanayake AP, Brys M, Glodzik-Sobanska L, de Leon MJ. Inflammation and Alzheimer's disease: possible role of periodontal diseases. Alzheimers Dement. 2008;4(4):242-50.

24. Noble JM, Scarmeas N, Papapanou PN. Poor oral health as a chronic, potentially modifiable dementia risk factor: review of the literature. Curr Neurol Neurosci Rep. 2013;13(10):384.

25. Oue H, Miyamoto Y, Okada S, Koretake K, Jung CG, Michikawa M, Akagawa Y. Tooth loss induces memory impairment and neuronal cell loss in APP transgenic mice. Behav Brain Res. 2013;252:318-25.

26. Miura H, Yamasaki K, Kariyasu M, Miura K, Sumi Y. Relationship between cognitive function and mastication in elderly females. J Oral Rehabil. 2003;30(8):808-11.

27. 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(4):596-600.

28. Kieser J, Jones G, Borlase G, MacFadyen E. Dental treatment of patients with neurodegenerative disease. N Z Dent J. 1999;95(422):130-4.

29. D'Hooge R, De Deyn PP. Applications of the Morris water maze in the study of learning and memory. Brain Res Brain Res Rev. 2001;36(1):60-90.

30. Watanabe K, Ozono S, Nishiyama K, Saito S, Tonosaki K, Fujita M, Onozuka M. The molarless condition in aged SAMP8 mice attenuates hippocampal Fos induction linked to water maze performance. Behav Brain Res. 2002;128(1):19-25.

31. Onozuka M, Watanabe K, Nagasaki S, Jiang Y, Ozono S, Nishiyama K, Kawase T, Karasawa N, Nagatsu I. Impairment of spatial memory and changes in astroglial responsiveness following loss of molar teeth in aged SAMP8 mice. Behav Brain Res. 2000;108(2):145-55.

32. Onozuka M, Watanabe K, Fujita M, Tomida M, Ozono S. Changes in the septohippocampal cholinergic system following removal of molar teeth in the aged SAMP8 mouse. Behav Brain Res. 2002;133(2):197-204.

33. Ono Y, Kataoka T, Miyake S, Cheng SJ, Tachibana A, Sasaguri KI, Onozuka M. Chewing ameliorates stress-induced suppression of hippocampal long-term potentiation. Neuroscience. 2008;154(4):1352-9.

34. Kordass B, Lucas C, Huetzen D, Zimmermann C, Gedrange T, Langner S, Domin M, Hosten N. Functional magnetic resonance imaging of brain activity during chewing and occlusion by natural teeth and occlusal splints. Ann Anat. 2007;189(4):371-6.

35. Ono T, Hasegawa Y, Hori K, Nokubi T, Hamasaki T. Task-induced activation and hemispheric dominance in cerebral circulation during gum chewing. J Neurol. 2007;254(10):1427-32.

36. Hasegawa Y, Ono T, Hori K, Nokubi T. Influence of human jaw movement oncerebral blood flow. J Dent Res. 2007;86(1):64-8.

37. Onozuka M, Fujita M, Watanabe K, Hirano Y, Niwa M, Nishiyama K, Saito S. Age-related changes in brain regional activity during chewing: a functional magnetic resonance imaging study. J Dent Res. 2003;82(8):657-60.

38. Grady C. The cognitive neuroscience of ageing. Nat Rev Neurosci. 2012;13(7):491-505.

39. Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich T. Globalepidemiology of dental caries and severe periodontitis - a comprehensive review. J Clin Periodontol. 2017;44 Suppl 18:S94-S105.

40. Kaye EK, Valencia A, Baba N, Spiro A, Dietrich T, Garcia R. Tooth loss and periodontal disease predict poor cognitive function in older men. J Am Geriatr Soc. 2010;58:713–718.

41. Kim J-M, Stewart R, Prince M, et al. Dental health, nutritional status and recent- onset dementia in a Korean community population. Int J Geriatr Psychiatry. 2007;22:850–855.

42. Stein PS, Kryscio RJ, Desrosiers M, Donegan SJ, Gibbs MB. Tooth loss, apolipoprotein E, and decline in delayed word recall. J Dent Res. 2010;89:473–477.

43. Chen JH, Lin LH, Chen YC. Risk Factors for dementia. J Formos Med Assoc. 2009;108:754–764.

44. Arrivé E, Letenneur L, Matharan F, et al. Oral health condition of French elderly and risk of dementia: a longitudinal cohort study. Community Dent Oral Epidemiol. 2012;40:230–238.

45. Stewart R, Stenman U, Hakeberg M, Hagglin C, Gustafson D, Skoog I. Associations between oral health and risk of dementia in a 37- year follow- up study: the prospective population study of women in Gothenburg. J Am Geriatr Soc. 2015;15:100–105.

46. Naorungroj S, Schoenbach VJ, Wruck L, et al. Tooth loss, periodontal disease, and cognitive decline in the Atherosclerosis Risk in Communities (ARIC) study. Community Dent Oral Epidemiol. 2015;43:47–57.

47. Tonetti MS, Van Dyke TE (2013) Working group 1 of the joint EFP/AAP workshop – periodontitis and atheroscle- rotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Dis- eases. Journal of Periodontology 84(4 Suppl), S24–9.

48. Cotti E, Mercuro G. Apical periodontitis and cardiovascular diseases: previous findings and ongoing research. Int Endod J. 2015;48(10):926-32.

49. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimers Dis. 2013;36(4):665-77.

50. Liu Y, Wu Z, Zhang X, Ni J, Yu W, Zhou Y, Nakanishi H. Leptomeningeal cells transduce peripheral macrophages inflammatory signal to microglia in reponse to Porphyromonas gingivalis LPS. Mediators Inflamm. 2013;2013:407562.

51. Wu Z., Nakanishi H., 2015. Lessons from microglia aging for the link between inflammatory bone disorders and Alzheimer's disease. J. Immunol. Res. 2015, 471342.

52. *Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, Nguyen M, Haditsch U, Raha D, Griffin C, Holsinger LJ, Arastu-Kapur S, Kaba S, Lee A, Ryder MI, Potempa B, Piotr Mydel2,6, Annelie Hellvard3,6, Karina Adamowicz2, Hatice Hasturk7,8, Walker GD, Reynolds EC, Faull RIM, Curtis MA, Dragunow M, Potempa J., 2019. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci. Adv. 2019; 5:eaau3333. **Most recent evidence is shown in terms of the association of Pg to AD.**

53. Arendt T, Brückner MK, Morawski M, Jäger C, Gertz HJ. Early neurone loss in Alzheimer's disease: cortical or subcortical? Acta Neuropathol Commun. 2015:10;3:10.

54. Foote SL, Bloom FE, Aston-Jones G. Nucleus locus ceruleus: new evidence of anatomical and physiological specificity. Physiol Rev. 1983;63(3):844-914.

55. Takahashi T, Shirasu M, Shirasu M, Kubo KY, Onozuka M, Sato S, Itoh K, Nakamura H. The locus coeruleus projects to the mesencephalic trigeminal nucleus in rats. Neurosci Res. 2010;68(2):103-6.

56. Maeda T, Byers MR. Different localizations of growth-associated protein(GAP-43) in mechanoreceptors and free nerve endings of adult rat periodontalligament, dental pulp and skin. Arch Histol Cytol. 1996;59(3):291-304.

57. Dandov AD, Atanasova DY, Lazarov, N.E. Morphological changes in the rat mesencephalic trigeminal nucleus following peripheral axotomy. Compt. Rend. Acad. Bulg.Sci. 2016;69(6), 801-806.

58. *Jou YT. Dental deafferentation and brain damage: A review and a hypothesis. Kaohsiung J Med Sci. 2018;34(4):231-237. **Possible explanation about the relationship between trigeminal neurodegeneration and the progress of dementia is shown.**

59. Xu X, Cao B, Wang J, Yu T, Li Y. Decision-making deficits associated with disrupted synchronization between basolateral amygdala and anterior cingulate cortex in rats after tooth loss. Prog Neuropsychopharmacol Biol Psychiatry. 2015;60:26-35.

60. Takeda Y, Oue H, Okada S, Kawano A, Koretake K, Michikawa M, Akagawa Y, Tsuga K. Molar loss and powder diet leads to memory deficit and modifies the mRNAvexpression of brain-derived neurotrophic factor in the hippocampus of adult mice.BMC Neurosci. 2016;17(1):81.

61. Oue H, Miyamoto Y, Koretake K, Okada S, Doi K, Jung CG, Michikawa M, Akagawa Y. Tooth loss might not alter molecular pathogenesis in an aged transgenic Alzheimer's disease model mouse. Gerodontology. 2016;33(3):308-14.

**Table 1.** Studies investigating the association between tooth loss and dementia. Published from 2014 to present only.

| Author, year (Reference) | Population | Results |
|---|---|---|
| Fereshtehnejad et al, (2018), [15] | 58,037 newly diagnosed individuals from the Swedish Dementia Registry and the Swedish Dental Health Register | Following dementia diagnosis, rate of dental care visits significantly declined. Individuals with mixed dementia, dementia with parkinsonism, and those with more severe and faster cognitive impairment had significantly higher rate of decline in dental care utilization. Vascular dementia and lower baseline Mini-Mental State Examination score were significant predictors of faster loss of teeth. |
| D'Alessandro et al., (2018), [16] | 120 AD patients (60 institutionalized in a public institute and 60 attended a daytime center). About 103 subjects formed the control group. | In the institutionalized subgroup, statistically more moderate and severe AD cases were detected and more patients were edentulous ($p < 0.001$). Noninstitutionalized patients presented DF/T ratio, CPI, and GI significantly lower ($p \leq 0.024$). |
| Okamoto et al., (2017), [19] | 3,061 community residents aged 65 years or older who had a score of 24 or more on the Mini-Mental State Examination. | Multiple logistic regression analysis using these items revealed that the odds ratio of 0–10 remaining teeth for mild memory impairment was 1.71 (95% CI 1.05–2.78), compared to individuals with 22–32 remaining teeth. A significant increase was found in a trend test to examine the increasing odds ratios of 22–32, 11–21, and 0–10 remaining teeth. |
| Takeuchi et al., (2017), [20] | Community-dwelling Japanese adults without dementia aged 60 and older (N = 1,566) were followed for 5 years | The risk of all-cause dementia was 1.62 times as great in subjects with 10 to 19 teeth, 1.81 times as great in those with one to nine teeth, and 1.63 times as great in those with no teeth as in those with 20 teeth or more. An inverse association was observed between number of remaining teeth and risk of AD (P for trend = .08), but no such association was observed with risk of VaD (P for trend = .20). |

AD: Alzheimer's Disease, D: decayed, F: filled, T: remaining natural teeth, CPI: community periodontal index, GI: gingival index, VaD: vascular dementia, CI: confidence interval.

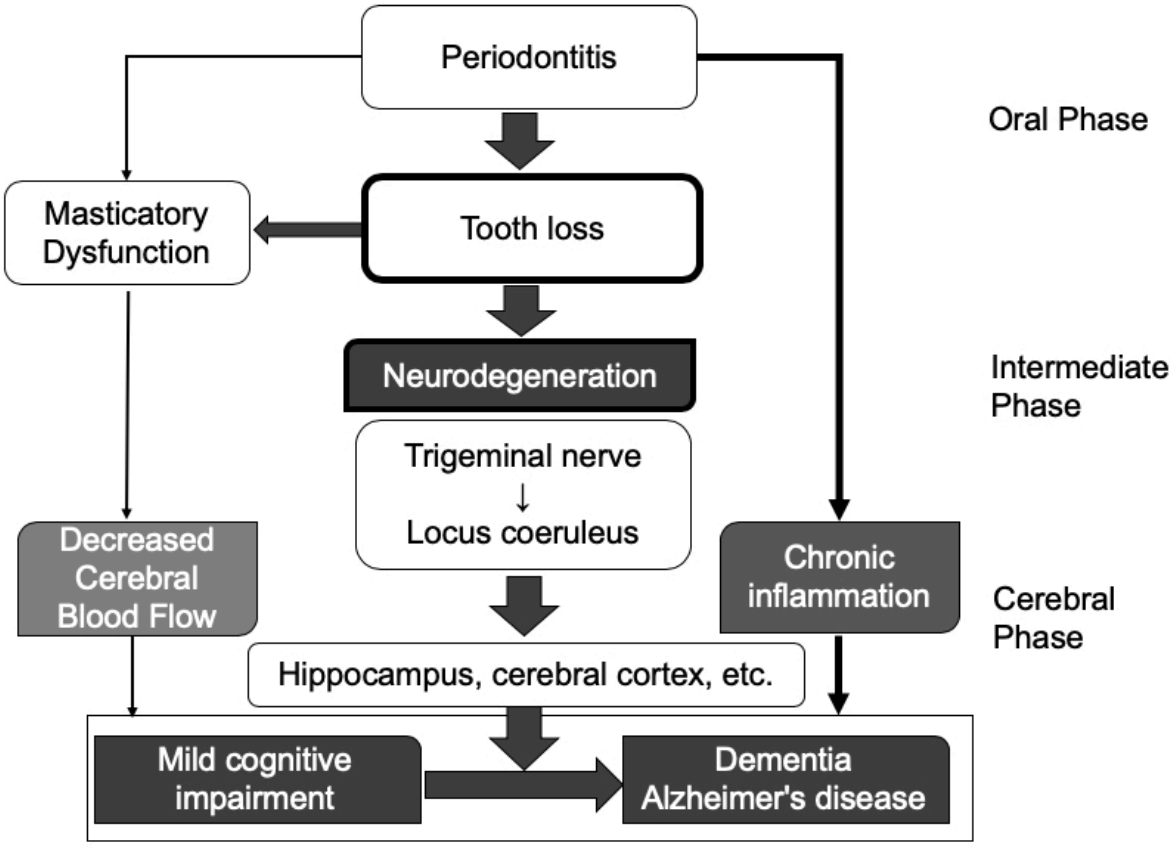


**Fig.1**
Schematic to show the effects of oral environments on the progress of dementia. Neurodegeneration by tooth loss directly accelerates the progress from mild cognitive impairment to dementia, whereas periodontitis and masticatory dysfunction indirectly involve in the progress of dementia.