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REVIEW ARTICLE

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Periodontal disease, tooth loss and dementia: Is there a link? A systematic review

Pallavi P. Tonsekar[1] | **Shuying S. Jiang**[2] | **Gang Yue**[1]

[1]Department of Periodontics, Rutgers School of Dental Medicine, Newark, NJ, USA

[2]Institutional Assessment and Quality Improvement, Rutgers School of Dental Medicine, Newark, NJ, USA

Correspondence
Pallavi P. Tonsekar, Department of Periodontics, Rutgers School of Dental Medicine, Newark, NJ, USA.
Email: pallavitonsekar@gmail.com

Background: It has been suggested that dementia is caused by neuronal damage due to chronic inflammation from peripheral sources such as the oral cavity in periodontal disease.

Objective: The aim of our review was to assess the risk of dementia or cognitive impairment associated with chronic periodontitis and multiple tooth loss.

Materials and methods: An extensive search of electronic databases of articles on the relation between periodontitis, tooth loss and dementia published on or before April 2016 was conducted. Experimental and human studies that provided a description consistent with multiple tooth loss, chronic periodontal disease and cognitive impairment obtained by validated methods were selected. The data extracted from the articles included study design, country of origin, sample size, methods used to assess periodontitis and cognition, average age at the baseline and number of years of follow-up. The Newcastle-Ottawa scale was used to assess the quality of human studies.

Results: The literature search yielded 756 articles which were independently screened, and 16 articles were included in the review. Four human studies reported an association of subsequent dementia with multiple tooth loss. One human study reported that chronic periodontal disease was associated with dementia. Eight experimental studies demonstrated an association between cognitive impairment and tooth loss.

Conclusion: The literature on chronic periodontitis and multiple tooth loss as risk factors to dementia remains inconclusive. More randomised clinical trials on the association between periodontitis and dementia with uniform criteria for evaluation and diagnosis of periodontitis are warranted.

KEYWORDS

chronic periodontitis, cognitive impairment, dementia, tooth loss

1 | INTRODUCTION

As the older demographic rises in the United States, there is growing interest in diseases that beleaguer elders. Dementia is a syndrome typically affecting the older population and exhibits progressive cognitive impairment.[1] As of 2016, the World Health Organization has estimated that 47.5 million people worldwide are diagnosed as having dementia.[2] This number is expected to increase to 75 million by 2030 and to 135 million by 2050.[1,3] Of the several types of dementia described, Alzheimer's disease (AD) is the most common, comprising 60%-70% of all dementias.[2] Symptoms of dementia include memory loss, confusion, difficulty in performing familiar tasks at home or in the workplace, and changes in behaviour.[2,3] As the disease progresses, the person experiences difficulty in performing neuromuscular actions such as swallowing, walking and even breathing.[4,5]

The pathogenesis of dementia has been a subject of great interest but is still not understood in its entirety.[6] Although certain forms of dementia which are caused by a reaction to drugs or infection may be treatable, the chronic forms of dementia that include AD, vascular and Lewy body dementia are progressive and irremediable[7-9] The role of inflammation in the pathogenesis of these forms of dementia has been suggested.[10,11] In consonance with this theory, inflammation causes neuronal damage in the form of a positively reinforced cascade of events in the central nervous system, beginning with stimulation of glial cells in the brain to produce pro-inflammatory cytokines such as C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-alpha), interleukin-1(IL-1) and interleukin-6 (IL-6).[10] These in turn stimulate the glial cells to produce pathologic protein molecules such as P-tau and Amyloid beta 1-42 peptide that ultimately cause nerve cell damage.[10-15] Pro-inflammatory mediators may enter the nervous system from peripheral sources such as the oral cavity via the blood brain barrier and/or by the stimulation of peripheral nerves, leading to amplification of inflammatory molecules in the central nervous system.[16-18]

Studies have indicated that chronic periodontitis may be one such peripheral source contributing to the evolution and progression of dementia.[16,19,20] It is well established that chronic periodontitis is caused by host response to predominantly gram-negative anaerobic bacteria.[21,22] Micro-organisms such as *Porphyromonas gingivalis*, *Agregatibacter actinomycetemcomitans* and spirochaetes release endotoxins such as lipopolysaccharides (LPS) which induce the production of TNF-alpha, IL-1, IL-6 and CRP in the blood.[23,24] At suitable concentrations, these bacterial endotoxins and inflammatory mediators trigger signalling pathways via toll-like receptor (TLR-2 and TLR-4) and integrin receptor complement-3 (CR3) mechanisms.[25] These in turn stimulate the release of cytokines from microglial cells which ultimately culminate in neurodegeneration.[25] Chronic periodontitis may form a covert interminable source for cytokines by upregulating a hyperinflammatory molecular cesspool which eventually finds its way in the central nervous system via vascular and/or neuronal pathways.[16,19,25]

Dementia has been reported to be associated with multiple tooth loss.[26,27] Whether tooth loss can be considered a measure of past periodontal disease needs to be further investigated.

Dementia impairs quality of life and life expectancy in advanced stages, causing grave emotional and economic impact on patients and their caregivers.[28,29] There is no known cure for dementia.[30] Thus, investigating the association between periodontitis and dementia might improve understanding of disease mechanisms and is therefore justified and warranted. Hence, a systematic review of the literature on the subject was undertaken. The purpose of this study was to review the literature on chronic periodontitis and tooth loss as risk factors for dementia or cognitive impairment.

2 | MATERIALS AND METHODS

This systematic review was conducted in adherence to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[31]

2.1 | Search strategy

Concurrent to a study that has shown[32] that using multiple databases is key to finding the maximum number of appropriate articles, we used electronic databases of Cochrane Library (Issue 12, 2015), PubMed (MEDLINE—1996), Scopus (1990) and Web of Science (1996). Our search was defined to identify articles published on or before April 2016 that demonstrated the association between chronic periodontitis, multiple tooth loss and dementia or cognitive impairment. Studies that provided a diagnosis congruent with chronic periodontal disease and tooth loss obtained by oral and radiographic examination were selected. Similarly, studies that established a definitive diagnosis of cognitive impairment or dementia by verified cognitive tests were selected. A search was conducted using MESH (medical subject heading) terms in different permutations and combinations: ("Periodontitis" [MESH] OR "Periodontal disease" [MESH] OR "chronic Periodontal disease" [MESH] OR "chronic periodontitis" [MESH]) OR ("tooth loss" [MESH]) AND ("Dementia" [MESH] OR "Cognitive Impairment" [MESH] OR "Alzheimer's disease" [MESH] OR "Alzheimer's" [MESH]). To broaden our search, we used free text which included "periodontitis," "periodontal disease," "chronic periodontitis," "tooth loss" and "dementia," "Alzheimer's disease," "Alzheimer's," "cognitive impairment" and "cognitive."

2.2 | Selection process

In the initial stage, after reading the titles, the abstracts of each study were reviewed. The full text of selected articles was then read. To broaden our search further, references lists of articles selected by the defined search protocol were manually searched. The search was conducted by all three authors (PPT, SSJ and GY) independently. In all cases, disagreements among the reviewers were resolved through discussion until a consensus was obtained. Final selection of studies was discussed, and worksheets to segregate the articles were made individually by all authors.

2.3 | Inclusion criteria

1. Studies dated up to April 2016 and published in English language script were included.
2. The exposures of interest were chronic periodontitis and tooth loss as assessed by oral examination and radiographic presentation.
3. Participants in human studies were individuals who were diagnosed with dementia or cognitive impairment. The outcome measured was assessed by verified cognitive tests such as Mini-Mental State Examination (MMSE), Delayed Word Recall (DWR) and Digit Symbol Substitution Test (DSST). There were no restrictions in age, socio-economic status, ethnicity or gender of individuals.
4. Experimental studies in which the exposure of interest was tooth loss or induced periodontal disease and the outcome was cognitive impairment as tested by immunohistochemical analysis and validated behavioural techniques such as maze and passive avoidance tests.

2.4 | Exclusion criteria

1. Studies which assessed the impact of dementia on oral hygiene measures, dental and periodontal health were not included as our aim was to analyse the reverse causal effect of chronic periodontal disease and tooth loss on prevalence and morbidity of dementia in subjects.
2. Studies with a cross-sectional design, as although demonstrating the association between the periodontal disease and dementia, they were unable to establish whether chronic periodontitis preceded dementia or occurred as a corollary of it.
3. Studies that did not establish cognitive impairment as the outcome and/or chronic periodontitis or tooth loss as the exposure of interest were excluded. Studies in which the diagnosis of periodontitis, tooth loss and/or cognitive impairment was based on information gathered from surveys, questionnaires and/or interviews rather than on clinical evaluation of the participants were also omitted.

A list of studies that were excluded during the selection process is available as a Appendix S1.

2.5 | Assessment of quality of articles

The quality of each human study was appraised using the Newcastle-Ottawa scale by each of the authors (PPT, SSJ and GY) individually. This scale helps evaluate the quality of studies in terms of design, selection and comparability of participant groups and assessment of outcome and exposure.[33]

2.6 | Data extraction

The data extracted from human studies included study design, country of origin, sample size, methods used to assess periodontitis, tooth loss and cognition, average age at the baseline and number of years of follow-up. In experimental studies, the data extracted included study design, species or strain of animals used, methods used to assess the exposure and outcome and duration of study.

3 | RESULTS

In total, the initial electronic search yielded 756 articles (Figure 1). After removing duplicate records, the abstracts of 85 remained for potential eligibility. At this stage, articles which reported the reverse effect of dementia on periodontal and oral health (n=12) and reviews (n=21) were excluded. The full text of remaining articles (n=52) was read. Studies that did not establish diagnosis of outcome and exposure measures by validated methods (n=28) and cross-sectional studies (n=11) were excluded. Articles which were extracted from bibliographies and relevant to the analysis were included in the review (n=3). In all, 16 articles were included in the systematic review.[26,34-48]

The complete list of articles excluded from the systematic review is presented as a Appendix S1.

3.1 | Characteristics of selected human studies

The descriptive analysis of selected articles is presented in Table 1. Eight human studies provided data from a combined population of 4075 participants in four countries.[26,34-40] Four were retrospective cohort,[26,34,38,39] three were prospective cohort,[35-37] and one was a case-control study nested in a longitudinal study.[40] Number of participants ranged from 144 to 911. Participant age had a wide range of 48-98 years.

All selected studies assessed periodontal health and tooth loss by clinical examination. Three studies assessed probing depths in participants.[35-37] Probing depth was measured from the base of the sulcus to

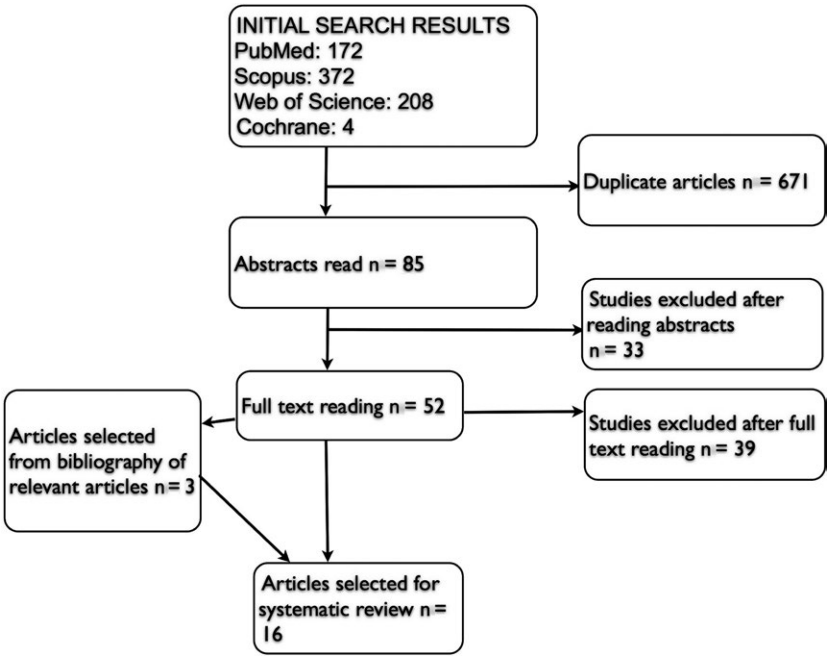

FIGURE 1 Selection process for systematic review

TABLE 1 Characteristics of studies on the association of periodontal disease, tooth loss and dementia

Study (y)	Study design	Country of origin	Dementia/CI assessed by	Periodontal health/tooth loss assessed by	Population
1. Stein[26] (2007)	Retrospective longitudinal	USA	AD by 1. MMSE test[a]; 2. Autopsied brain matter of deceased for neurofibrillary tangles	1. Tooth loss by oral examination 2. Radiographic alveolar bone loss	144 F
2. Kim[40] (2007)	CC[c] nested in a longitudinal study	S.KOREA	Dementia by MMSE, DSM-IV[d] criteria	Tooth loss, denture use by oral examination	686 (281F, 405M)
3. Stein[38] (2010)	Retrospective longitudinal	USA	AD by DWR[e]	Tooth loss by clinical examination	144 F
4. Chen[34] (2010)	Retrospective longitudinal	USA	Dementia by clinical evaluation using International Classification of diseases.	Calculus, plaque deposits, Bleeding on probing, tooth loss by dental records	491 372 Controls (110M 262F) 119 cases (30M 89F)
5. Kaye[35] (2010)	Prospective Longitudinal	USA	Cognitive impairment by MMSE, SCT[f] tests	1. Periodontal health by Oral examination, probing depths, alveolar bone height by radiographs; 2. Tooth loss evaluated.	597 M
6. Arrivé[36] (2012)	Prospective Longitudinal	FRANCE	DSM-III criteria for dementia. Type of dementia assessed.	Teeth by DMFT[g], occlusion Periodontal status by CPI[h] index	405, (184 M, 221F)
7. Stewart (2015)[39]	Retrospective longitudinal	SWEDEN	Dementia, cognitive impairment by MMSE	Tooth loss by clinical examination	158 F cases 539-F controls
8. Naorunroj[37] (2015)	Prospective longitudinal	USA	Cognitive Impairment by DWR DSS, WF	Oral examination at baseline visit; tooth loss, Probing depths, dental plaque gingival crevicular fluid assessed.	911 (556 M 355 F)

[a]Mini-Mental State Examination test used in diagnosis of cognitive impairment and dementia with maximum score of 30. Scores<24 indicate cognitive impairment.
[b]Apolipoprotein E allele, accepted risk factor for Alzheimer's disease.
[c]Case-control study design.
[d]Diagnostic and statistical Manual for mental disease 4th ed.
[e]Delayed word recall test for dementia of Alzheimer's disease type. Lower scores indicate cognitive impairment.
[f]Spatial copying test for cognitive impairment. Scores range from 0-26. Lower scores indicate cognitive impairment. In this study, scores were obtained for analysis between 1993-2001.
[g]Decay, missing, filled teeth Index.
[h]Community periodontal index.

the gingival margin. There was considerable diversity in the definition and method of evaluation of periodontal disease among these studies. The Biofilm Gingival Index (BGI)[37] was used in one study, and Community Periodontal Index (CPI) was used in another.[36] Periodontitis was variously defined as one or more sites with probing depths >4 mm[37] and an increase in probing depths of 2 mm bone loss of at least 40% from baseline.[35] In another study, alveolar bone loss on radiographs was assessed;[26] participants who had 4-6 mm of alveolar bone loss in 33% or more of their teeth and who had >6 mm in 33% or more of their teeth were considered to have moderate and severe periodontitis, respectively.

Avg. age at base line (BL)	No. of years at follow-up	Results	Comments
83 y	21 y	Greater tendency to develop incident Dementia in subjects with greater tooth loss. Periodontitis not related to incidence of dementia	Study a part of the NUN study performed on Roman Catholic nuns. Hence a homogenous cohort with similar lifestyle and diet. Alveolar bone height from radiographs used to assess periodontal status. ApoE[b] genotype was assessed as modifying factor.
70-74 y	2.8 y	Lower tooth count associated with dementia especially in those without dentures	Nutrition was affected in those with less number of teeth. However no association between dementia and nutrition was found. Insufficient timeline for assessment of cognitive decline ApoE genotype not considered.
84 y	Mean-21 y	Tooth loss associated with lower delayed word recall test scores.	Homogeneous study Sample. APoE genotype assessed.
Healthy 74±11 y Dementia 81.5±9 y	7 y (mean 38.8 mo)	Tooth loss nor periodontal condition associated with cognitive impairment. Greater accumulation of calculus, plaque at baseline in dementia subjects than in controls.	Significant disparity in ages of cases and controls.
48 y	32 y	Advanced tooth loss and periodontal disease increased risk of lower cognitive scores.	Substantial observation period. Study conducted on men only. Baseline information on cognition status not available. ApoE genotype not assessed as modifying factor.
70 y	15 y	Having less teeth remaining was associated with a lower risk of dementia. Finding was significant only in dementia with lower educational background. CPI scores had no effect on cognitive impairment	The only study that found a negative association between tooth loss and dementia. However CPI scores were not associated with cognitive impairment. Study did not establish an association between masticatory function and cognitive impairment.
Average 80 y at last visit.	37 y	Tooth loss was not associated with lower cognition after adjusting for age, socioeconomic factors	Type of dementia (AD, vascular) assessed. Substantial follow-up period.
64.7±4.3 y	8 y	Lower cognitive scores associated with completely edentulous subjects. Periodontitis, oral hygiene not associated with cognitive function.	Oral examination performed only at baseline.

Eight studies evaluated tooth loss as an exposure of interest[26,34-40] (Table 2). In general, tooth loss was described as advanced if 0-10 teeth were remaining[26,34-40] during examination.

All eight studies had cognitive impairment, dementia or AD as the outcome of interest.[26,34-40] The tests used to establish cognitive impairment in these studies was MMSE, DWR, DSST, Block Design Test (BDT), Boston Naming Test, Word Fluency Test and Wechsler Adult Intelligence Scale (WAIS). Lower test scores indicated cognitive impairment.

Quality assessment of studies according to Newcastle-Ottawa criteria is presented in Table 3. Five studies had a follow-up of

TABLE 2 Tooth loss as exposure of interest in human studies

Name of study	Assessment of tooth loss
Stein 2007	Categorised as 0, 1-9,10-6 and 17-28 teeth remaining.
Kim 2007	Categorised as 0,1-4,15-24,25-27,28+ teeth remaining.
Kaye 2010	Tooth loss rate defined as teeth lost per decade of follow-up.
Chen 2010	Categorised as 0,1,2,3-4,5-6,7-8, all teeth lost.
Stein 2010	Categorised as 0-9 or 10 or more teeth remaining.
Arrive 2012	Categorised as <4, 4-11,11-19, more than 19 teeth missing.
Naorungroj 2015	Number of teeth and complete edentulism evaluated.
Stewart 2015	Categorised as 0,1-14,15-24,25-27,28+ teeth remaining.

more 10 years;[26,35,36,38,39] three had a duration of <10 years.[34,37,40] Three studies determined the presence of apolipoprotein E (ApoE) allele[26,37,38] which is considered a major genetic risk factor for Alzheimer's disease and a possible confounding factor in the association between periodontitis and dementia.[49] All selected articles adjusted for demographic factors such as age and gender; however, none considered race as a possible modifying factor. One study assessed oral hygiene habits of patients.[34] The population in four studies comprised of either males[35] or females.[26,38,39] The remainder of studies reported no variation in outcomes between genders.[36,37,40]

3.2 | Association between chronic periodontitis, tooth loss and cognitive impairment

It was reported by Kaye et al.[35] that chronic periodontitis as determined by probing depths and attachment loss was associated with low cognitive scores in participants. Cognitive impairment increased with progressive alveolar bone loss (spatial copying test: HR=1.03, CI=1.01, 1.06) and increased probing depths (MMSE test: HR=1.04, CI=1.01, 1.09; spatial copying test: HR=1.04, CI=1.01, 1.06).[35] Naorungroj (2015) reported that DWR and WF test scores at follow-up visits were lower in edentulous participants compared to dentate participants although no association was found between periodontal disease and cognitive impairment.[37]

TABLE 3 Evaluation of study quality using modified Newcastle-Ottawa scale

Study										Total
Cohort/longitudinal	A[a]	B[b]	C[c]	D[d]	E[e]	F[f]	G[g]	H[h]	I[i]	Total max. 9
Stein 2007		*	*	*	*	*	*	*	*	8
Chen 2010	*	*	*			*	*		*	6
Stein 2010		*	*	*	*	*	*	*	*	8
Kaye 2010	*	*	*			*	*	*	*	7
Arrivé 2012	*	*	*	*		*	*	*	*	8
Naorungroj 2015	*	*		*	*	*	*		*	8
Stewart 2015	*	*	*	*		*	*	*	*	8
Case control	A[j]	B[k]	C[l]	D[m]	E[n]	F[o]	G[p]	H[q]	I[r]	Total max. 9
Kim 2007	*	*	*	*		*	*	*		7

[a]Representativeness of the exposed cohort- representative of the average population.
[b]Selection of the non exposed cohort- drawn from the same community as the exposed cohort.
[c]Ascertainment of exposure (Periodontitis and/or tooth loss)- clinical evaluation; serum analysis of antibodies to periodontopathic micro-organisms.
[d]Demonstration that outcome (dementia/cognitive impairment) was not present at the start of the study.
[e]Study controls for APoE genotype.
[f]Study controls for additional factors (socioeconomic factors, smoking, diet, etc.)
[g]Assessment of dementia- independent blind assessment/record using validated assessment tools such as MMSE, DWR tests.
[h]Was follow- up long enough for outcomes to occur? (≥10 y).
[i]Adequacy of follow-up- all subjects accounted for.
[j]Is the case definition adequate, with independent validation?
[k]Representativeness of the cases- consecutive or obviously representative series of cases.
[l]Selection of controls- from community.
[m]Definition of controls- no history of dementia.
[n]Study controls for APoE genotype.
[o]Study controls for additional factors (socioeconomic factors, smoking, diet etc.)
[p]Ascertainment of exposure (Periodontitis and/or tooth loss)- clinical evaluation; serum analysis of antibodies to periodontopathic micro-organisms.
[q]Same method of ascertainment for cases and controls.
[r]Non response rate- same rate for both groups.

Four studies reported an association between multiple tooth loss and lower cognitive scores.[26,37,38,40] It was reported that risk of low MMSE and spatial copying scores increased with each tooth lost per decade since baseline dental examination (HR=1.09, 95% CI=1.01, 1.18 and HR=1.12, CI=1.05, 1.18, respectively).[35] In a 37-year study, Stewart et al.[39] reported that dementia was two to three times more prevalent in females with fewer than nine teeth than in those with 25 or more teeth. However, after adjusting for various confounding factors, no association was found between tooth loss and cognitive impairment.[39] One study reported that in late-middle-age adults, complete edentulism was associated with lower cognitive scores, although tooth loss was not associated with subsequent cognitive impairment.[37] On the other hand, one prospective longitudinal study reported that tooth loss of >11 teeth was associated with a lower risk of dementia in participants with lower school level education (HR= 0.3 95% CI:0.11-0.79).[36]

3.3 | Characteristics of selected experimental studies:

The characteristics of experimental studies are presented in Table 4. All studies had control groups or "no extraction groups." [41-48] Four studies used senescence-accelerated mouse prone 8 (SAMP8) mice.[43,44,47,48] Two studies used male Wistar rats to conduct the experiments:[42,49] one used transgenic mice[46] and one used Sprague Dawley rats.[41] Number of animals used ranged from 17 to 128. Six studies had molar or tooth loss as exposure of interest,[41-43,45,47,48] whereas two studies were based on loss of masticatory ability by cutting off the crown portion of molars at the gingival margin.[44,46]

Spatial memory and learning ability were tested using maze tests in seven studies[41,42,44,46-48] and passive avoidance tests in two studies.[41,43] Immunohistochemical analysis of the hippocampal region of the brain was conducted in the studies. Mice of young-, middle- and old-age groups were tested in two studies.[43,47]

3.4 | Association between tooth loss and cognitive or memory impairment in the experimental models

The studies reported a reduction in the correct responses and an increase in number of errors in the spatial memory tests following molar extraction.[41-48] Yamazaki (2008)[48] and Andoh (2009)[41] reported that the errors in spatial memory tests increased with the number of teeth lost and that response latency was proportional to tooth loss. In two studies, it was shown that age-dependent loss of memory occurred in the experimental groups.[43,47] It was reported that learning and spatial memory impairment increased with time following tooth loss.[48]

A significant reduction in hippocampal density and number of neurons following tooth loss and chewing ability was reported in studies, and an increase in the number of astrocytes and astroglial hypertrophy in the hippocampus was demonstrated.[43,47] Further, hippocampal induction of the Fos protein, which is the corresponding protein for c-Fos gene responsible for neural plasticity and is expressed in the hippocampus following spatial and learning performance, was reduced in aged mice following tooth loss.[46] Interestingly, both learning scores and induction of the Fos gene into the hippocampus improved after replacing the crowns of cut molars with artificial crowns.[46]

4 | DISCUSSION

The oral cavity, particularly in chronic periodontal disease, provides a rich source of inflammatory molecules in the blood. Kamer, Noble, Singhrao and Stein are leading a growing body of researchers exploring the association between periodontal disease and dementia.[6,16,25,26] Aside from the incontestable theory that advanced cognitive impairment may cause difficulty in performing oral hygiene measures and would result in periodontal disease and tooth loss,[50,51] there are multiple possible mechanisms in which periodontal health can conversely affect cognitive function:(i) chronic periodontitis may provide a peripheral source of pro-inflammatory cytokines,[6,16,25] (ii) nutritional habits may change due to tooth loss and periodontal disease.[37] A diet low in antioxidants, vitamins B and E, and high in unsaturated fats has been suggested to contribute in the development of dementia.[52,53] (iii) The association may be confounded by socio-economic and environmental factors that affect the prevalence and progression of both diseases such as age, history of depression, stress, alcoholism and smoking.[54] Diseases such as diabetes, hyperlipidaemia and cardiovascular diseases that mainly affect the older population may further modify the expression of either or both of these diseases.[55,56]

4.1 | Tooth loss, periodontal disease and dementia

Tooth loss can be associated with dementia in various ways. (i) Chronic periodontal disease as evidenced by multiple tooth loss may provide a continual source of pro-inflammatory mediators,[6,16] (ii) Tooth loss may lead to reduced masticatory forces which in turn diminishes cerebral blood flow and proprioception to the brain.[57-60]A lack of masticatory forces and chewing difficulty has also been associated with impaired cognitive function.[61] Gatz[62] observed in identical twins discordant for dementia that greater tooth loss under the age of 35 years was associated with subsequent dementia. On the other hand, Arrive et al.[36] noted that tooth loss reduced the risk of cognitive decline in participants with lower level of education. This finding may be reflective of reduced inflammatory burden in patients with less number of teeth. If tooth loss is considered to be largely due to, and hence a good measure of, past periodontal disease, then it would imply that completely edentulous patients are more periodontally compromised than dentate patients where significant clinical attachment loss and periodontal inflammatory burden has been established. However, tooth loss may be caused by a multitude of reasons besides periodontal disease.[63-65] Other confounding factors such as nutrition, systemic disease and socio-economic factors further complicate the association. Hence, tooth loss may be positively or negatively associated with periodontal disease. It is interesting to note that none of the studies investigated the cause of tooth loss in study participants. Whether

TABLE 4 Characteristics of experimental studies on the association between tooth loss and cognitive impairment

Name	Species	Randomised?	Control?	Sex	Number	Exposure of interest	Outcome of interest
1. Kato 1997[42]	Aged Wistar rats	No	Yes	Male	Controls (non tooth loss group)- 9 Experimental (tooth loss)- 10	Molar/tooth loss by extraction	Spatial memory using radial arm maze, and AChl[a] release into parietal cortex by microdialysis method.
2. Onozuka 1999[44]	Aged SAMP8[b] mice	No	Yes	Male	2 groups: 10 control 10 experimental	Molar loss, mastication; crowns of molars were cut off.	Spatial memory by water maze, quantitative assessment of neurons in hippocampus
3. Onozuka 2000[43]	SAMP8 mice	No	Yes	Male	34 young, 94 aged	Tooth loss by extraction of maxillary molars.	Spatial memory using Morris water maze. Changes in GFAP[c] expression in the hippocampal formation
4. Watanabe 2002[46]	Aged SAMP8 mice	No	Yes	Male	96 total	Lack of chewing ability by cutting off maxillary molar crowns at gingival margins. Restoration of chewing ability by fitting artificial crowns.	Exp 1 and 2: Spatial memory by Morris water maze, immunohistochemical analysis of hippocampal formation. Exp 3: Spatial memory by water maze test after restoration of chewing ability using artificial crowns.
5. Yamazaki 2008[48]	7-wk-old Wistar rats	No	Yes	Male	TL1 bilateral first molars extracted=18 TL2 bilateral first and second molar extraction=18 TL3 all three molars extracted=18	Molar/tooth loss by extraction	Spatial memory by radial maze; No of hippocampal pyramidal cells and TrkB-mRNA[d] in brain.
6. Andoh 2009[41]	7-wk-old Sprague-Dawley rats	Yes	Yes	Male	90 total 6 groups based on extraction and type of test 15 in each group	Molar loss. Rats underwent unilateral (1st, 2nd and third molars) or bilateral (1st 2nd and third molars) or no extraction (controls)	Cognition using maze experiment and passive avoidance experiments
7. Watanabe 2001[47]	SAMP8 mice	No	Yes	Male	Young=30 6 mo age=30 Old group=30	Molar loss by extraction of maxillary molars	Spatial memory by Winter Maze test. Analysis of hippocampal formation, neuronal degeneration and glial fibrous acidic protein (GFAP) expression in the hippocampus following molar loss.
8. Oue 2013[45]	Transgenic mice	No	Yes	Female	17 total Control-7 Exp- 10	Tooth loss	Learning and memory by Passive avoidance tests. Amyloid beta deposition and changes in neuronal number in the hippocampus region of brain.

[a]Acetyl choline.
[b]Senescence Accelerated Mouse Prone 8.
[c]Glial fibrillary acidic protein.
[d]TrkB-mRNA- Tropomyosin receptor kinase -B
[e]BDNF- Brain derived Neurotrophic factor

Duration of study	Findings	Observations.
135 wk	Number of errors were increased and correct responses was reduced in toothless rats. Extracellular ACh of the molarless rats was significantly low compared to that of the control aged rats.	Impairment of spatial memory in the molarless aged rats may be due to the functional deterioration of the cholinergic neuronal system induced by tooth loss.
10 d	Molarless mice had reduced learning and memory in water maze experiment. Reduced density in hippocampal area in molarless mice compared to controls.	Study demonstrated relation between loss of chewing ability due to tooth loss and decrease in number of neurons. Lack of mastication rather than tooth loss was the exposure of interest.
7 d	Tooth loss caused an increase in hypertrophy and number of astrocytes. Significant reduction in learning ability water maze test compared with controls. Adrenal gland density was greater in experimental mice suggesting higher corticosterone levels.	Stress caused by pain from extractions, rather than tooth loss or loss of masticatory ability may have induced astroglial hypertrophy.
17 d	Suppressed learning ability caused after tooth loss was restored following fitting of artificial crowns.	Study showed that induction in the hippocampus of Fos protein linked to spatial memory was reduced following loss of chewing ability.
7-8 wk	Spatial memory and number of trkB-mRNA-positive cells were both negatively affected by the duration of tooth loss and the number of teeth extracted.	TrkB-BDNF[e] binding is a mediator of hippocampal dependent learning and memory. This study suggests that tooth loss reduces sensory input to the hippocampus from receptors linked to mastication related movements of jaws in rats.
10 d	Increase in tooth loss led to greater errors among groups. Number of errors significantly less in controls than in bilateral molar extraction groups. When extractions increased, response latency increased.	Learning/memory evaluation using passive avoidance and maze.
17 d	Age dependant. decrease in learning ability and number of neurons in hippocampal region following tooth loss. Age-dependent increase in the number and hypertrophy of GFAP-labelled astrocytes in the hippocampus was greater in tooth loss group than in non tooth loss (control) groups	Three age groups of mice were used. This study demonstrated that spatial memory impairment induced by tooth loss began in middle age and increased with old age. Tooth loss did not appear to cause spatial memory deficits in young mice.
10 mo	At 10 mo of age, learning ability decreased in experimental group. Neuronal cells in hippocampal region also reduced as compared to control group. No significant difference in amyloid levels between the groups.	Tooth loss did not enhance amyloid deposits; hence it may cause learning and memory impairment by direct induction of atrophy of pyramidal cells.

tooth loss signifies a reduction or an increase in inflammatory burden merits further discussion and behoves future studies to ascertain the cause of tooth loss in study participants.

The lack of uniformity in the method of periodontal evaluation among the studies, and in the definition of chronic periodontitis impeded in forming a consolidated assessment of the cause effect relation between the two diseases and precluded the possibility of a meta-analysis. As per the 2003 Center of Disease Control (CDC) and American Academy of Periodontics (AAP) workshop, clinical attachment loss provides for greater accuracy and uniformity in defining periodontal disease,[66] as probing depths and clinical attachment loss are truer representatives of current and cumulative disease, respectively.

4.2 | Inflammatory theory and role of periodontitis in the etiopathogenesis of dementia

Studies have shown that nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) delay the onset of dementia, supporting the inflammatory theory of dementia.[67,68] As described by Singhrao and Kamer, the stimulation of glial cells is central in the development of the disease by triggering the release of pro-inflammatory cytokines which form amyloid plaques and foment vascular damage.[16,25]

Miklossy was one of the first to demonstrate spirochaetes in brain matter, cerebrospinal fluid and blood of patients with Alzheimer's disease.[69,70] Various species of Treponema including *T. denticola* have been found in the trigeminal ganglia of patients with AD,[71] a finding reflective that one of the routes of oral infection to the brain may be via the branches of the trigeminal nerve. The presence of *P. gingivalis* lipopolysaccharide in brain specimens of patients with AD has also been reported.[72] Virulence factors of *P. gingivalis*, *T. denticola* and *A. actinomycetemcomitans* such as gingipain and lipopolysacharides are known to attack the endothelium of vessel walls.[73] It is possible that endothelial dysfunction, initiated by these periodontopathic factors, may eventually cause dementia.[74]

Chronic periodontitis has an inflammatory profile similar to diseases such as atherosclerosis and smoking.[75,76] Vascular endothelial dysfunction appears to be the mainstay in the pathogenesis of these diseases.[75] Thus, periodontitis and systemic diseases, such as atherosclerosis, stroke and obesity which are also linked to dementia,[77] may converge to form a common pathway, ultimately leading to neurodegeneration.

It has been established that genetic make-up may be at play in the expression of Alzheimer's disease (AD).[12,78] Of the several phenotypes considered, the apolipoprotein E (ApoE) e4 allele is most strongly associated with increased susceptibility to AD and is regarded as a major risk factor.[12,16,78,79] In the present review, three articles assessed ApoE genotype of participants as a possible confounding factor in the association between periodontitis and dementia.[26,34,37] Few studies considered history of depression,[36] use of drugs such as benzodiazepenes and anticholinergics, diet[40] oral hygiene habits,[34] smoking[35-37] and alcohol consumption,[35,36,38] basal metabolic rate (BMI)[35-37,39] and physical activity of the participants. It is possible that these factors may have affected the outcomes reported in these studies.

4.3 | Experimental studies on the association between tooth loss and cognitive impairment

Although the murine model has been used for several decades in ageing research, the senescence-accelerated mouse prone 8 (SAMP8) has the advantage of rapid ageing due to accelerated physiological senescence, causing its lifespan to be an average of 12 months, that is about half of that of a rodent.[80] Further, some ageing behavioural characteristics and histopathology resemble those of Alzheimer's disease in humans.[80] Studies have used SAMP8 mice of young-, middle- and old-age groups to demonstrate the varying effects of tooth loss at different ages.[43,47] Watanabe[47] reported an age-dependent increase in the errors in spatial memory and learning tests in middle- and old-age experimental groups. Onozuka[43] noted that the association between memory impairment and tooth loss was not prevalent in young mice.

The hippocampal region of the brain plays a pivotal role in spatial memory and learning and is one of the first regions to show morphological and physiological changes in ageing, with increase in the number of astrocytes and glial fibrillary acidic protein (GFAP) and a decrease in neurons.[81] Studies have demonstrated an increase in (GFAP)-labelled astrocytes and astroglial hypertrophy in the hippocampus following tooth loss.[47] There are various possible mechanisms that link tooth loss to changes in the hippocampus. Tooth loss may cause reduced sensory impulses related to mastication and jaw-related movements to the somatic sensory cortex which provides circuits between the neo-cortex and the hippocampus.[82] Kato[42] demonstrated a decrease in the acetyl choline (ACh) release from the cerebral cortex in aged rats following molar extraction. Okuda reported a decrease in glutaminic acid release from the hippocampus following tooth loss.[83] Yamazaki used the expression of trkB-mRNA to illustrate reduced synaptic transmission levels in the pathways related to learning and memory.[48] Thus, disruption of the central cholinergic system may be another possible mechanism by which tooth loss causes hippocampal dysfunction in aged mice.

It is interesting to note that in some studies reviewed, the effect of loss of chewing ability rather than tooth loss was demonstrated by cutting off the crowns of molars at the gingival margin.[44,46] Tooth loss implies that loss of the periodontal ligament is the main reason for reduced sensory input, whereas masticatory input from jaw muscles and the temporomandibular joint is reduced following cutting molar crowns at the gingival margins.

The adrenal glands of experimental mice were found to be heavier following tooth loss in one study.[43] Since neural damage and glioisis have been associated with increased levels of corticosteroids and stress, it is possible that the memory and learning impairment caused by tooth loss may have occurred due to stress from pain following extractions or cutting of the molars.[46] However, it was also demonstrated that the number of errors in memory tests and astroglial dysfunction increased with time in aged mice.[48] Further, hippocampal dysfunction and spatial memory impairment were not seen in young mice following similar extraction protocol.[43,47] Hence, it is unclear whether or not pain-related stress could have contributed to the findings.

Taken together, experimental studies suggest a link between tooth loss, memory and learning impairment. Although it is not always straightforward to translate experimental findings to human research, animal models nevertheless provide valuable insight into the ageing process and aid in understanding the pathogenesis of age-related diseases such as dementia and Alzheimer's disease.

Because dementia has been associated with increased morbidity and mortality and because of the ubiquity of periodontitis and tooth loss, consolidated evidence and an improved understanding of the relation between the two may have important public health implications. The authors underscore the importance of uniformity in methods used to establish the diagnosis of chronic periodontitis and the ascendant need of more studies on the association between the two diseases with adequate duration and sample power. More controlled randomised studies that provide data on the history of periodontal status before dementia has been established are warranted.

5 | CONCLUSION

Analysis of the literature on the association between subsequent dementia, periodontal disease and tooth loss was inconclusive. Results of this study should be interpreted with caution. More randomised clinical trials on the association between these chronic diseases with uniform diagnostic criteria should be conducted.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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