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REVIEW ARTICLE

Tooth loss, periodontal infection and their relationship to cognitive impairment and other dementias: A review.

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Abstract

Our review study addresses the issue of tooth loss, which is caused by loss of masticatory function and its impact on cognitive functions, dementia, and Alzheimer's disease. Numerous studies have confirmed a positive correlation between premature tooth loss, reduction in masticatory function and significant cognitive decline observed through learning disabilities, including overcoming ordinary life problems to early and advanced forms of dementia. Reduced numbers of teeth in the main food processing area, i.e., loss of large molars, have been implicated as a possible cause of cognitive impairment. In research in this area, some groups of major etiopathogenetic causes of this issue have also been established. A significant etiopathogenetic cause of tooth loss is the disappearance of their mechanoreceptors in the periodontium, causing the disappearance of sensorimotor excitation via the cranial nerve V and the associated atrophic changes in the trigeminal brain nuclei and their branching in the Locus Coeruleus area. It may cause further neurodegenerative involvement in this area, one of the centers of the adrenergic system involved in cognitive function. Relatively well-studied factors are the lack of blood supply to the cerebral area during inadequate mastication caused by loss of molars and the consequent hypoxia of brain and nerve structures. In the research and development of Alzheimer's disease, there have been many recent references to the fact that the primary bacterium causing periodontitis, *Porphyromonas gingivalis*, can infect the neurons of the cranial nerve V ending close to the Locus Coeruleus and thus tau proteins, after tooth extractions, can spread to other subcortical nuclei in the brain. These findings are of great relevance to clinical practice in dentistry as we strive to prevent tooth loss in the distal compartment, which is made possible by the tremendous expansion of endodontic techniques and technologies to save de facto every tooth and its periodontium with the mechanoreceptors necessary to preserve sensorimotor nerve excitability and sensorimotor nerve networks. We uncompromisingly eliminate every periodontal infection in the subgingival region as part of our preventive-therapeutical procedures.

INTRODUCTION

Intact cognition is one of the pillars of human adaptive mechanisms enabling continuous adaptation to changing surroundings and social environment. Cognitive impairments, including their most severe forms such as dementias, have different etiologies and their frequency increases with advancing age. In the human population, the most common causes of severe dementia are Alzheimer's disease (AD), vascular dementia (VaD), Parkinson's disease, and the sequelae of dramatic cerebrovascular diseases. However, there are prodromal stages in different types of severe dementias that also manifest cognitive decline (Sabayan & Sorond, 2017). It is well known from clinical practice that cognitive decline persists longer before the actual symptoms and diagnosis of dementia and may not be immediately associated with some severe forms of dementia (Mattson *et al.* 2009). Among the systemic and social risk factors for cognitive decline, age, gender, hypertension, hypercholesteremia, diabetes mellitus, ischemic heart disease, lifestyle, level of education and dietary habits are most commonly cited. These factors may underlie milder cognitive disorders, such as impaired learning and memory impairment (Han *et al.* 2022).

COGNITIVE DISORDERS AND TOOTH LOSS

Results of epidemiological studies

It is well known that the condition of the periodontal tissues is crucial for adequate transmission of masticatory pressure. For this reason, several substantial studies have focused on their health status and possible cognitive impairment. The highest validity in assessing this issue is represented by their electronic treatment in the form of meta-analytical studies. A meta-analytical study by Asher *et al.* (2022) compiled 47 scientific studies dealing with poor periodontal status in association with cognitive decline and 23 other studies discussing the association between a damaged periodontium and the development of various types of dementia. Cognitive decline with an OR (odds ratio) of 1.23 was associated with polymorbidity of the hinge tooth apparatus in the form of periodontitis and deep periodontal pockets with bone destruction to complete tooth elimination. Suppose we want to transform these values into understandable language. In that case, we can state that patients with affected periodontium have a 1.23 times higher probability of developing a disease from the spectrum of cognitive impairment.

Losses in cognitive parameters and functions such as concentration and memory in patients with extensive tooth loss causing masticatory deficits have been studied using large-scale data from two public surveys in the United States presented as NHANES (2005-2008) and NHIS (2014-2017). These studies included 102,291 individuals, and, to the greatest extent possible, more potential etiologic cofactors represented by age, education, and adverse socio-economic status were eliminated. By statistically comparing the defective occlusion and impaired masticatory ability of these subjects, it was evaluated in correlation with the level of cognition and the occurrence of anxiety states. It was determined that **among the significant predictors of cognitive functions, we could include the reduced number of teeth present in the mouth.** This association showed a graded effect regarding inverse proportionality, i.e., the lower the number of teeth in the mouth, the more severe cognitive decline (Galindo-Moreno *et al.* 2021). Meta-analytic evaluations through electronic searches represent their highest method of assessment. Relevant matched cohort studies from PubMed, Web of Science, and Embase databases were included in 18 statistical evaluations of 356,297 subjects with a mean follow-up of 8.6 years. The pooled RR (relative risk) of tooth loss in dementia was 1.15, and the pooled RR of tooth loss in cognitive decline was 1.20. Relative risk is an index describing the relationship between exposure to a risk factor and its consequence, i.e., it is a ratio in the exposed and unexposed set, and at values >1, it is a risk factor. Thus, applying it to our issue, we can conclude that tooth loss is a risk factor for dementia and cognitive decline with RR values of 1.15 and 1.20, respectively (Li *et al.* 2023). However, during extensive research, there were reported studies that did not confirm the mentioned correlations (Arrivé *et al.* 2012).

Causal links between tooth loss and cognitive impairment and dementia – a review of studies

Various scientific studies have dominated the research domain investigating causal links between premature tooth loss and cognitive impairment, mainly conducted in animal models and studies. In an electronic search since 2010, 26 of these studies were included in the overall evaluations according to uniformly determined criteria. **The evaluation of causal possibilities between extensive tooth loss and cognitive impairment, including their most severe conditions in the form of dementia, can be grouped into four effective, relatively well-distinguishable etiopathogenetic groups of problems.** A summary of the above issues is addressed in the extensive study by Wang *et al.* (2022). Many of the scientific studies in this area are cited below and can be divided into 4 clusters of problems: **a.** Reduced receptor-afferent stimulation conditioned by periodontal tissue loss may disrupt connections between neural pathways, impairing the relevant brain regions. **b.** Tooth loss leads to impaired motor function of the masticatory muscles, decreasing their load and blood flow in the cerebral area. **c.** Tooth loss may stimulate an independent factor of neurodegeneration by increased accumulation of β-amyloids in the brain. **d.** Tooth loss and impaired neural pathway function exacerbate some neurodegenerative changes. In our

review study, we will discuss the causal links from the first two groups in detail.

a. After tooth extractions, the periodontal tissues with all nerve endings and mechanoreceptors disappear, causing the disappearance of afferent receptor excitation through the trigeminal network, which stimulates some changes in the brain and causes a decline in cognitive function. The preservation of mechanoreceptors in the periodontium and alveolar bone is a significant predictor of the preservation of masticatory abilities of chewing muscles (Brodin *et al.* 1993; Türker *et al.* 2007). Preserving masticatory abilities is essential for fast and appropriate cognitive reactions and responses (Hirano *et al.* 2012), with mastication reducing latencies of relevant potentials related to external stimuli and increasing vigilance (Sakamoto *et al.* 2015). The entry of the trigeminal nerve into the brain around the pons Varoli has both acute and long-lasting effects on the brain and its cognitive functions. New knowledge in the field states that these effects are made possible by a trigeminal influence on the Locus Coeruleus (LC), which is a nucleus in the posterior area of the rostral pons Varolii in the lateral floor of the fourth ventricle and is an organ of the ascending reticular activating system (ARAS) and a site of norepinephrine secretion. Together with the adrenal medulla it forms the noradrenergic system (De Cicco *et al.* 2017).

The disappearance of mechanoreceptors in the periodontium and alveolar bone results in the attenuation of receptor-afferent stimulation of the corresponding neural pathways to the brain and the disappearance of their mutual interactions, and the target brain regions may degenerate (Wang, 2022). With the loss of occlusal functions, not only one brain region responsible for nutrition is damaged, but distant connections between the anterior cingulate cortex (ACC) and the basolateral amygdala (BLA) may also be affected, which has been found by EEG evaluation in rats after molar extraction. Furthermore, it was found that theta frequency, a characteristic signal for cognition, was not synchronous between the ACC and BLA regions, clearly indicating the weakening of the strength of neural networks (Xu *et al.* 2015).

Even though lack of masticatory function or soft food feeding are considered risk factors for cognitive decline and dementia, final and definitive conclusions between insufficient orofacial sensorimotor activity and cognitive impairments are currently not well defined or established (Oue *et al.* 2013). However, the decline in sensorimotor innervation and activity after tooth extractions is reduced through the weakening of neural networks and the attenuation of the influence of the nervus trigeminus on the Locus Coeruleus (Xu *et al.* 2015; De Cicco *et al.* 2017). The extent to which physiological sensorimotor innervation, starting with receptors in the periodontium, can be replaced by implant-prosthetic treatments of edentulous jaws is sought to be explained by some studies with unilaterally extracted teeth using the facts that on the side with lost molars, there were narrower pupils and lower EMG values after jaw clenching. These differences between the dentate and non-dentate sides of the dentition in the different pupil responses and lower EMG activity were significantly reduced after implant-prosthetic treatment of the unilateral defect. According to the authors of this study, the cause of cognitive impairment in unilateral tooth loss may be due to unequal trigeminal activity of paired Locus Coeruleus, which impairs cognition. The study indirectly suggests that types of implant-supported prosthetic restorations may reduce the imbalance of proprioceptive afferent nervus trigeminus stimuli as evidenced by a reduction in pupil size asymmetry and improve sensorimotor afferent stimulation of the cranial nerve V (De Cicco *et al.* 2016; De Cicco *et al.* 2017). However, findings from one or a few observational studies cannot be used to conclude whether implant-supported prosthetic solutions can replace periodontal proprioceptor-activated sensorimotor excitations of the trigeminal nerve in the periodontium.

b. Tooth loss results in decreased motor function of the masticatory muscles, which reduces blood flow in the cerebral region. The intact masticatory function has a direct positive effect on perfusion and the natural oxygen supply to the brain. During mastication, the following brain regions were particularly activated: the principal nucleus of the nervus trigeminus, the thalamus, the frontotemporal complex, the subcortical caudate nuclei, and the cerebellum. Increased blood flow during mastication was observed in pyramidal pathways in the hippocampus, cerebral context in the somatosensory area, and several motor areas (Tsutsui *et al.* 2007; Viggiano *et al.* 2016; Yokoyama *et al.* 2017). Some studies report that adequate mastication may prevent cognitive impairment (Li *et al.* 2023) and Alzheimer's disease through its beneficial effect of increased vascular supply to the central nervous system (Miyake *et al.* 2012). However, tooth loss causes deficits and reduction of some brain structures (Minn *et al.* 2013). Laboratory rats subjected to tooth extractions in the molar region showed decreased blood flow in areas responsible for cognition. They increased glutamate concentration and expression of several genes responsible for apoptosis in the hippocampal CA1 region after 12 weeks (Luo *et al.* 2019). In another animal experiment, the loss of molars caused reductive volumetric changes in the brain (Avivi-Arber *et al.* 2016). Although several studies have found a beneficial effect of mastication on blood flow in the cerebral region, few have shown direct correlations between mastication and cognitive impairment and their interpretation should be cautious (Lin, 2018). An association defined as the "brain-stomatognathic axis" that can be activated by physiological mastication has recently been reported in investigating the relationship between masticatory function and cognitive functions. This connection is a complicated mechanism

consisting of a complex neural network movement in multiple brain regions, including prefrontal cortical areas (Yokoyama *et al.* 2017).

Other predominantly inflammatory factors in the periodontium associated with cognitive loss and the development of Alzheimer's disease

Impact of pathological colonization of subgingival spaces

Chronic periodontitis is a severe disease of the alveolar bone, periodontal ligaments, and periodontal soft tissues. It is characterized by an extraordinary accumulation of anaerobic infection in the space of periodontal pockets. From these well-vascularized subgingival spaces, which are under mastication pressure, predominantly Gram-negative anaerobic bacteria, a wide range of pro-inflammatory cytokines, and various immunocompetent cells are continuously released into the circulating blood. Destructive periodontitis has a systemic impact on the whole organism as a systemic inflammatory disease of low but long-lasting character, disseminating bacteria and inflammation to all tissues and organs (D´Aiuto *et al.* 2005; Straka, 2011; Straka *et al.* 2011). Currently, a wealth of knowledge is accumulating on the Gram-negative anaerobic bacterium *Porphyromonas gingivalis*, which produces destructive and immune-stimulating virulence factors such as lipopolysaccharide endotoxin, several capsular antigens, and two groups of proteolytic destructive enzymes, which are **gingipains R (RgpA, RgpB) and gingipains K (Kgp), having enormous penetrative power to infiltrate neurovascular and other systems.** Their highly pathogenic potential lies in their potent proteolytic action, and they are characterized as trypsin-like cysteine proteinases and collagenases produced by all strains of *Porphyromonas gingivalis* (McAlister *et al.* 2009). The major virulence factors of *P. gingivalis* and their etiopathogenetic potential have been the subject of many studies dealing with the onset of AD (Watts *et al.* 2008; Singhrao & Olsen, 2019). Gingipains can degrade, catabolize, and deactivate arginine and lysine molecules, which are components and parts of the immunological defense barrier (Singhrao & Olsen, 2019). These Arg-gingipains and Lys-gingipains are not inactivated by a group of intrinsic protease inhibitors such as alpha-antichymotrypsin and cystatins, which facilitates their invasion of the host (Singhrao *et al.* 2017). *Porphyromonas gingivalis* can invade and persist in neurons. Thus, invaded and infected neurons show several signs of AD-associated neuropathological changes such as increased ratio of cytoskeletal breakdown, increased ratio of phosphorylated tau protein to normal tau protein, loss of synapses, accumulation of autophagic vacuoles and multiple vesicular bodies as well as destruction of the cytoskeleton (Ilievski *et al.* 2018). The Gram-negative anaerobe *Porphyromonas gingivalis* activates and stimulates the proteolytic activity of the enzyme cathepsin B, which conditions the breakdown (APP) of the amyloid-β precursor protein and the formation of amyloid plaques. Some studies have shown that tau protein and actin, present in the structure of axons and dendrites, can be a substrate for gingipain Kgp produced by *P. g.* (Poole *et al.* 2013).

The mentioned virulence factors of the primary microbial pathogen of chronic destructive periodontitis, which is *Porphyromonas gingivalis* in cooperation with other anaerobic bacteria of the subgingival environment, cause the disintegration and destruction of healthy subgingival biofilms with commensal bacteria and the formation of a pathological biofilm in the sense of a dysbiome or pathobiome. The pathobiome in the subgingival area is a massive source of circulating pro-inflammatory mediators and acute inflammatory markers. In investigating the impact of destructive periodontitis and its effect on memory and dementing conditions, including Alzheimer's disease, several groups of possible etiopathogenetic associations have been established with varying penetration to the issues. A critical group of causal factors is the formation of the pathobiome in the subgingival environment and its impact on dementia and Alzheimer's disease (Kamer *et al.* 2008; Ishida *et al.* 2017).

Other factors of tooth loss may also be involved in cognitive impairment, among which destructive periodontitis dominates with its enormous infectious potential in the form of some virulence factors of the bacterium *Porphyromonas gingivalis*, which has an affinity for nervous tissue. Striking findings have been presented in this area. In investigating the etiopathogenesis of Alzheimer's disease, current science is engaged with a few working hypotheses. Some of them focus on the fact that patients with the acquired (sporadic) form of Alzheimer's disease have an unaltered or wild-type gene for the production of APP. From this perspective, the pathway of AD development is being investigated and studied, which suggests a reduced or defective clearance of amyloid plaques through cathepsin B, to which *P. gingivalis* infection may contribute. The long-term colonization of the subgingival spaces of periodontal pockets and the subsequent invasion of *P. gingivalis* through the disrupted oral epithelium into the cells of the organism is a sequence of several "subtle" steps that allow the bacterium to bypass the immunological defense of the cells and the organism. *P. gingivalis* penetrates intracellularly into lysosomal cell bodies through the endoplasmic reticulum. Its virulence factors can alter lysosomal enzymes, disrupting various signaling molecules and connections associated with several major overall diseases (Dorn *et al.* 2001; Zhang *et al.* 2018), including periodontitis (Olsen & Yilmaz, 2016), Alzheimer's disease (Wu *et al.* 2017), or coronary vascular diseases (Dorn *et al.* 2001). Significant experiments in laboratory mice have confirmed that *P. gingivalis* infection can actively enter intracerebrally following failure or weakening of the encephalic brain barrier. Specifically, the evidence for

entry of the identical strain of *P. gingivalis* that induced infection in the periodontium has been directly demonstrated in some brain cells by multiple methodologies (Ilievsky *et al.* 2018; Singhrao *et al.* 2017; Goto & Leung, 2019; Goto *et al.* 2020). The results of some experiments conclude that familial genetic conditioned Alzheimer's disease represents increased deposition of insoluble Aβ plaques, and the sporadic form represents rather defective clearance of this insoluble protein. Neuropathological symptoms are characterized by a certain latency period estimated to be 10 years, which would correlate with the statements that patients exposed to a 10-year duration of periodontitis are at risk of developing the sporadic form of Alzheimer's disease. This approximately 10-year "delay" in disease onset is explained by the slow failure of the encephalic barrier and the gradual intracerebral penetration of inflammation, thus confirming the 10-year duration of periodontitis as a significant and novel risk factor for the development of Alzheimer's disease for these patients. The causal link between tau protein phosphorylation and *P. gingivalis* infection explains the development of both forms of Alzheimer's disease through the studies described above. *P. gingivalis* and its LPS initiate inflammatory signaling and cognitive impairment in the early stages of infection and can later penetrate intracerebrally and develop Alzheimer's disease (Noble *et al.* 2009; Singhrao & Olsen, 2019; Ilievski *et al.* 2018; Olsen & Singhrao, 2018; Ding *et al.* 2018; Ide *et al.* 2016; Wu *et al.* 2017).

CONCLUSION

The retention of mechanoreceptors in distal teeth in the periodontium is the origin of the receptor-afferent connection between the masticatory system in the jaws and its termination in the trigeminal nuclei in the pons Varolii, which are connected by a neural network to some cerebral nuclei associated with cognitive functions. After tooth extractions, the motor-afferent trigeminal innervation and the neural pathways and connections associated with it disappear, which has a damping and inhibitory effect on the Locus Coeruleus, a component and part of cognitive functions. Significant tooth loss and subsequent destruction and disruption of trigeminal afferent pathways and their neuronal networking in the central nervous system in laboratory animals resulted in the loss of dendritic pyramidal cells and shrinkage of grey matter in cortical areas and the basal ganglia of the brain. All these structures are part of cognitive functions and processes, and their subsequent disruption was manifested in several parameters of impaired cognition.

The number of experiments and studies cited above also justify us in concluding that premature tooth loss, occlusion disorders and impaired masticatory ability can adversely affect multiple cognitive functions, ranging from learning disabilities to severe forms of dementia, including Alzheimer's disease, by several possible mechanisms. The current state of knowledge in this area highlights the vital role of masticatory muscle function on perfusion and blood flow to the cerebral area confirming that intact mastication is one of the basal factors for preserving intact cognition and preservation of molar mastication may be a predictive factor for its maintenance.

Significant findings were also made in animal models with laboratory mice with genetically induced Alzheimer's disease in which molars were extracted. In immunohistochemical analysis after neuronal death of the extinct n. trigemini in the brain, a lot of cytotoxic Aβ42 amyloid substances were released from the brain into its surroundings, intoxicating the nearby Locus Coeruleus, where the beginnings of Alzheimer's disease are described, which is considered as one of the possible causal factors in the onset of Alzheimer's disease. Implications for clinical practice lie in the knowledge that patients with a predisposition to develop AD may experience an acceleration of disease onset after tooth extractions. Tooth loss is most commonly associated with various inflammatory-destructive periodontal diseases. The subgingival pathobiome in periodontitis containing *P. gingivalis* can causally predispose its carriers to develop Alzheimer's disease after several years of periodontal disease, as proteolytic destructive enzymes of *P. g.* named gingipains can invade and persist in neurons. Gingipains stimulate the proteolytic properties of another enzyme, cathepsin B, which causes the breakdown of the amyloid-β protein precursor and the formation of amyloid-insoluble plaques. These new findings are essential for exploring new directions and paths in the investigation of etiopathogenetic causes of Alzheimer's disease. The prevention and treatment of premature tooth loss in the molar region, which ensures sufficient mastication, is essential for clinical practice. For clinical practice, the preservation of periodontal tissues with their pressure receptors or nerve endings, which, by sensorimotor connections through neural pathways, terminate in the brainstem and provide afferent neural networks of tissue neurons is essential. Another crucial preventive factor is preventing and treating destructive periodontitis by sophisticated debridement of the subgingival environment and eradicating major periodontal pathogens, including *Porphyromonas gingivalis*, by professional and home hygiene.

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