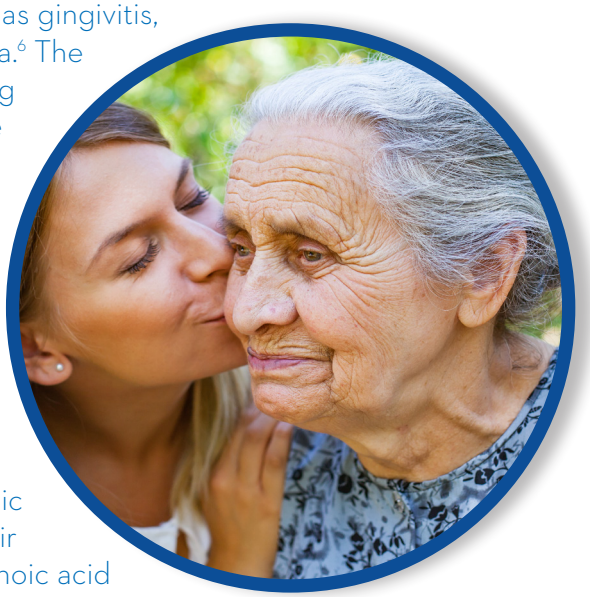
Role of Oral Hygiene in the Management of Gingivitis and Implications for Patients with Alzheimer's Disease and Impaired Cognitive Function

Microbial Etiology of gingivitis - a plaque induced inflammation of the gingiva. Progressive periodontal diseases are a significant burden to oral health worldwide.[1] In addition to tooth loss, chronic periodontal diseases are increasingly suggested as significant factors in development and/or progression of a variety of systemic conditions including cardiovascular disease, diabetes, rheumatoid arthritis, Alzheimer's disease and pre-term births.[2-5] Periodontal disease initially presents as gingivitis, a plaque induced inflammation of the marginal and attached gingiva.[6] The clinical symptoms of gingivitis include redness, edema, and bleeding at the gingival margin. Demonstration that periodontal diseases are of microbial origin was proven by landmark experimental gingivitis (EG) studies in the 1960s, which demonstrated that the suspension of oral hygiene resulted in rapid dental plaque formation.[7-9] Left undisturbed, maturation of the dental plaque over time inevitably produced gingival inflammation, albeit with variable onset and progression. The microbial composition of dental plaque during the development of gingivitis was associated with proliferation of Gram negative bacteria when assayed by culturing techniques.[10-12] Pathogens associated with gingivitis display unique metabolic activities (production of hydrogen sulfides and short chain carboxylic acids[13] and express lipopolysaccharides (LPS's) or endotoxins in their cell walls.[14-15] The LPS from Gram negative bacteria, and the lipoteichoic acid produced by some Gram positive pathogens can be considered to be a major factor in the pathogenesis of progressive periodontal diseases.[16]



Gingivitis is a risk factor for a more advanced form of periodontal disease, periodontitis. Gingivitis precedes the development of progressive periodontal disease. The clinical symptoms of gingivitis include redness, edema, and bleeding at the gingival margin. Gingival bleeding, an objective measure of inflammation has been positively correlated to histologic changes in the gingiva, which include a greater percentage of cell-rich collagen-poor connective tissue consistent with an inflammatory infiltrate, as compared to non- bleeding sites.[17] The clinical significance of gingival bleeding should not be underestimated, as chronic inflammation of the gingiva and periodontium has been shown to be a significant risk factor for both periodontal attachment loss and recession. Sites with persistent gingival bleeding over multiple periodic examinations have been shown to have higher odds for progressive attachment loss compared to non- bleeding sites.[18] Over a 26-year observation period in a population of well- maintained, well-educated men who practiced regular oral hygiene, sites that bled consistently throughout the course of the study had approximately 70% more attachment loss than sites that were consistently noninflamed, yielding an odds ratio of 3.22 for inflamed sites (bleeding) converting to attachment loss.[18] These persistent bleeding sites can exist even if patients are considered generally healthy. In addition, the absence of persistent gingival bleeding on probing has also been shown to have a high negative predictive value of 98.1% for disease progression, as measured by ≥2 mm attachment loss, in a periodontal maintenance population over a 2.5-year observation period.[19] The established relationship between persistent gingival bleeding and attachment loss is the mechanistic basis for gingival inflammation as a risk factor for tooth mortality. Importantly, teeth surrounded by persistent inflamed gingival tissue (presence of bleeding) had a 46-fold higher risk of being lost over a 26-year observation period, compared to teeth surrounded by inflammation-free gingival tissues (absence of bleeding).[20]

Patients with Alzheimer's Disease and impaired cognitive function have a higher risk for developing poor oral hygiene and periodontal disease. It has been estimated that there were 35.6

million individuals with dementia (loss of cognitive function) worldwide in 2010 and that number will double every 20 years, reaching >115 million people by 2050.[21] Foley et al. 2017; published a systematic review with meta-analyses examining the oral health status of patients with dementia and reported that patients with dementia have significantly worse oral hygiene with a standardized mean difference = 0.88 (95% CI:0.57-1.19; p<0.0001).[22] Furthermore, patients with dementia have significantly worse periodontal disease with a standardized mean difference = 0.38 (95% CI:0.06-0.70; p=0.02).[22] Gil-Montoya et al., 2015 published a case control clinical study examining the oral health status of 180 patients with dementia relative to 229 patients without dementia and reported that patients with dementia have significantly worse oral hygiene with a standardized mean difference = 1.033 (95% CI:0.826-1.241; p<0.001).[23] Furthermore, patients with dementia have significantly worse periodontal disease (percent of sites with >3 mm attachment loss) with a standardized mean difference = 0.329 (95% CI:0.133-0.526; p<0.001).[23]

This relationship is bi-directional, with the presence of periodontitis increasing the risk for Alzheimer's Disease and impaired cognitive function. Chen et al., 2017 published the results of a retrospective matched cohort study examining the association between chronic periodontitis exposure over a 10 year period and the risk of developing Alzheimer's Disease in 9,291 patients with newly diagnosed periodontitis and 18,672 matched healthy control patients who did not have periodontitis.[24] Patients with chronic periodontitis were at higher risk of developing Alzheimer's Disease relative to the healthy controls with an adjusted Hazard Ratio = 1.707 (95% CI:1.152-2.528; p=0.0077).[24] Ide et al., 2016; published a 6 month longitudinal cohort study comparing 20 patients with Alzheimer's Disease and periodontitis to 32 patients with Alzheimer's Disease and no periodontitis and reported a statistically significant 6-fold increase in the rate of cognitive decline (Alzheimer's Disease Assessment Scale: ADAS-cog) in the Alzheimer's patients that had pre-existing periodontitis over a 6 month period.[25] Tzeng et al.; 2016 published the results of a retrospective cohort study comparing 2,207 patients with periodontitis to 6,621 healthy control patients and reported that patients with periodontitis were more likely to develop dementia with an adjusted Hazards Ratio = 2.54 (95% CI:1.297-3.352).[26] Lee et al., 2017 published the results of a prospective cohort study comparing 3,028 patients with periodontitis to 3,028 healthy control patients and reported that patients with periodontitis were more likely to develop dementia with an adjusted Hazards Ratio = 1.16 (95% CI:1.01-1.32).[27] Kamer et al., 2012 published the results of a retrospective cohort study comparing patients with periodontal infection to healthy control patients and reported that patients with periodontal infection were more likely to develop loss of cognitive function (digital symbol scores) with an odds ratio = 7.00 (95% CI:1.74-28.16).[28]

Periodontal bacteria infect the brain and play a direct role in amyloid brain lesions in Alzheimer's Disease. Kamer et al., 2015 published a cross-sectional clinical study involving 38 patients and reported an association between periodontal disease (attachment loss > 3 mm) and an increase in amyloid plaque pathology in the brain in the form of increased uptake of 11c-PIB in amyloid B vulnerable regions of the brain (p=0.002).[29] Amyloid plaque pathology in the brain is a central feature of Alzheimer's Disease. Noble et al., 2009 published a cross-sectional clinical study in 2355 patients and reported that patients with high levels of IgG antibody specific to Porphrymonas gingivalis (>119 Elisa units) were more likely to have loss of cognitive function as measured by poor delayed verbal recall with an odds ratio = 2.89 (95% CI:1.14-7.29) and impaired subtraction with an odds ratio = 1.95 (95% CI:1.22-3.11) compared to the patients with low P.gingivalis IgG (<57 Elisa units).[30] Noble et al., 2014; published a case cohort study in 219 patients (110 Alzheimer's patients and 109 healthy control patients) and reported that patients with high levels of Actinomyces naeslundi specific IgG (>640 ng/ml) was associated with an increased risk of Alzheimer's Disease with an unadjusted Hazards Ratio = 2.0 (95% CI:1.1-3.8) and an adjusted (for other IgG titers) Hazards Ratio = 3.1 (95% CI:1.5-6.4).[31] Ding et al., 2018 published a randomized controlled study in mice demonstrating that infecting mice through the oral delivery of P.gingivalis results in impairment of cognitive function (learning & memory function) of infected middle aged mice (12 months old).[32] Dominy et al., 2019 published a series of experiments demonstrating that: 1.) P.gingivalis gingipain enzymes (RgpB & Kgp) are found in >90% of brain tissue biopsies from Alzheimers Disease patients using monoclonal anitibodies to detect RgpB (51/53 patients) and Kgp (49/54 patients), 2.) RgpB and Kgp brain loads are correlated to Tau pathology and cause Tau degradation in a dose dependent manner which is related to amyloid plaque formation, and 3.) P.gingivalis DNA is present in the cerebrospinal fluid of 70%

(7/10) of clinical Alzheimer's Disease patients supporting an infection of the brain.[33] In ensuing mice studies, Dominy et al reported that: 1.) all 8 mice infected orally with P.gingivalis over a 6 week period ended up with P.gingivalis infection of brain tissue, 2.) that P.gingivalis brain infection is predicated on functioning RgpB and Kgp gingipain enzymes, as P.gingivalis with knockout RgpB and Kgp genes did not promote brain infection, and 3.) a specific Kgp gingipain inhibitor COR271 administered orally reduced P.gingivalis load in the brain in infected mice.[33]

SnF2 is an effective antimicrobial in plaque and gingivitis control. The management of gingivitis can be attained through repeated mechanical removal of microbial dental plaque from the teeth and/or suppression of bacterial plaque biofilm growth and metabolism. The mechanical control of plaque is accomplished with daily oral hygiene including thorough tooth brushing and flossing. The suppression of plaque growth and metabolism can be achieved through the application of topical antimicrobials added to toothpastes or mouthrinses. Antimicrobials with proven efficacy for the control of plaque associated gingivitis include chlorhexidine, cetypyridinium chloride, mixtures of essential oils, triclosan and stannous fluoride, among others.[34,35] The use of stannous fluoride for the treatment and prevention of plaque and gingivitis began in the 1980's with the application of topical gels, however today its use includes multiple commercial dentifrices sold and distributed around the world.[36-38] Clinical studies have demonstrated significant efficacy of stannous fluoride for the reductions in the amount of supragingival plaque and plaque associated gingivitis – these having been the subject of systematic reviews of randomized clinical studies.[39-41] A recent meta-analysis revealed that during Crest Pro Health (CPH) stannous fluoride dentifrice use 3 out of 4 participants using CPH transitioned to gingival health[42] as defined by guidelines for the 2017 World Workshop of Periodontology.[43] The results of this meta-analyses representing 18 studies in 2,890 patients support that stannous fluoride dentifrices reduce gingival bleeding sites by 51% relative to sodium fluoride control dentifrices in studies of up to 3 months duration.[42]

Stannous fluoride has both, bactericidal and bacteriostatic effect on plaque bacteria. Recently, it has been demonstrated that dentifrice SnF2 can penetrate into subgingival crevicular fluid during brushing and stannous is retained in subgingival plaque.[44] This SnF2 has been shown to decrease biofilm virulence via attaching to lipopolysaccharide (LPS) and lipoteicoic acid (LTA) molecular patterns on bacterial surfaces interfering with pathogen stimulation of toll receptors[45,46] the latter of which are associated with the initialization of the inflammatory processes involved in periodontal disease.[47-52] Samples of plaque from subgingival areas in subjects brushing with stannous fluoride dentifrice have been shown to exhibit decreased virulence ex vivo.[53,54] In addition, stannous fluoride formulations have been shown to reduce bacterial metabolic products including short chain fatty acids propionic and butyric acid which are derived from bacterial metabolism in deeper parts of plaque biofilms in anaerobic environments.[55] Collectively, research demonstrates significant efficacy for stannous fluoride for the treatment and prevention of gingivitis and has established plaque control including quantity and toxicity as mechanisms for clinical efficacy.

Role of SnF2 in plaque and gingivitis control in patients with Alzheimer's Disease. There are numerous studies showing that the prevalence, progression, severity, and extent of chronic oral diseases are significantly increased in increased in Alzheimer's Disease patients. The main oral complications associated with Alzheimer's Disease, include infection of the gums, periodontal disease, tooth decay, dry mouth, and halitosis. Alzheimer's Disease and associated conditions resulting in loss of cognitive function often worsens oral health, particularly that of the gum tissues. Due to the risk of Alzheimer's Disease patients experiencing progressive periodontal diseases, it is more important for these patients to develop and maintain good oral hygiene. This often requires third party delivery of oral care. The patient and dental professional must work together to stop this Alzheimer's cycle before it begins by being attentive to daily oral hygiene: brushing and flossing, getting regular oral health checkups, and properly treating periodontal disease early on. Oral hygiene in Alzheimer's Disease patients can be improved by increased education on the requirements for elevated oral hygiene and also by the selection and application of selective oral products applied to their personal hygiene. The causative factors for gingivitis in Alzheimer's Disease patients, toxic plaque can likely be ameliorated by improved hygiene including the selection and use of antimicrobial products with proven efficacy in the

prevention of plaque and gingivitis. The use of stannous fluoride dentifrice as part of oral hygiene may represent a useful tool for Alzheimer's Disease patients in maintaining their oral health.

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