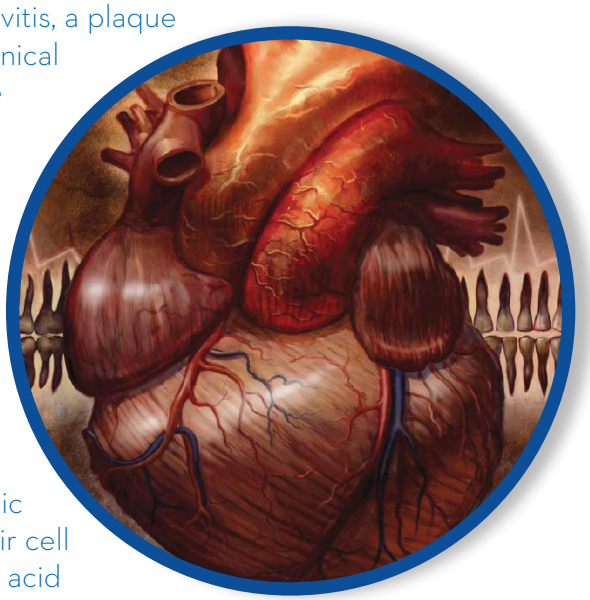
Role of Oral Hygiene in the Management of Gingivitis and Implications for Patients with Cardiovascular Disease

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, 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 periodontitis have an increased risk for cardiovascular disease. A number of systematic reviews with meta-analyses have reported that patients with periodontal disease are at increased

risk for cardiovascular disease. Blaizot et al, 2009 reported the outcomes of 29 studies in 167,931 patients, finding that periodontal disease increases the risk of cardiovascular disease (myocardial infarction, angina pectoris, coronary artery disease) with an OR = 2.35 (95% CL:1.87-2.96) in 22 observational studies and an OR = 1.34 (95% CL:1.27-1.42) in 7 cohort studies.[21] Xu et al, 2017 reported the outcomes of 22 studies in 129,630 patients, finding that periodontal disease increases the risk of myocardial infarction (heart attack) with an OR = 2.02 (95% CL:1.59-2.57).[22] Martin-Cabezas et al, 2016 reported the outcomes of 15 studies in 1,072,582 patients, finding that periodontal disease increases the risk of arterial hypertension with an OR = 1.50 (95% CL:1.27-1.78).[23] Zeng et al, 2016 reported the outcomes of 15 studies in 17,330 patients, finding that periodontal disease increases the risk of carotid atherosclerosis with an OR = 1.27 (95% CL:1.14-1.41).[24] Wang et al, 2019 reported the outcomes of 25 studies in 22,090 patients, finding that periodontal disease increases the risk of peripheral artery disease (as measured by ankle brachial index or carotid intima-media thickness) with an OR = 1.60 (95% CL:1.41-1.82).[25] Humphrey et al, 2008 reported the outcomes of 7 studies in 35,681 patients, finding that periodontal disease increases the risk of coronary heart disease with an OR = 1.24 (95% CL:1.01-1.51).[26] This study also reported a similar non-significant trend for gingivitis increasing the risk of coronary heart disease with at OR = 1.35 (95% CL:0.79-2.30) based on 2 studies with 9,458 patients.[26] The results of this study were generally consistent with Bahekar et al, 2007, who reported that periodontal disease increases the risk of coronary heart disease in 5 cohort studies in 86,092 patients with an RR = 1.14 (95% CL:1.07-1.21), in 5 cross-sectional studies in 17,724 patients with an OR = 1.59 (95% CL:1.33-1.91) and in 5 case-control studies with 1,423 patients with an OR = 2.22 (95% CL:1.59-3.12).[27] Janket et al, 2003 reported the outcomes of 9 studies with 107,011 patients, finding that periodontal disease increases the risk of cardiovascular disease with a RR = 1.19 (95% CL:1.08-1.32) and increases the risk of stroke with an RR = 2.85 (95% CL:1.78-4.56).[28] Fagundes et al, 2019 reported that periodontal disease increases the risk of stroke with a RR = 1.88 (95% CL:1.55-2.29) in 7 cohort studies and increases the risk of ischemic stroke with a RR = 2.72 (95% CL:2:00-3.71) in 4 case-control studies.[29]

Periodontal therapy in the form of subgingival scaling and root planing improves cardiovascular endpoints. Scaling and root planing is the preferred dental procedure performed to reduce subgingival periodontal inflammation. A number of systematic review meta-analyses have reported that controlling local periodontal infection and inflammation through scaling and root planning has systemic effects on cardiovascular endpoints. Roca-Millan et al, 2018 reported the outcomes of 10 clinical trials in 669 patients and found that periodontal therapy (OHI, supragingival scaling, SRP) decreases serum CRP (C-reactive protein) by 1.199 mg/l (95% CL:1.100-1.299) relative to no treatment based on the 4 studies that had this endpoint and comparison.[30] The manuscript also reported that periodontal therapy (OHI, supragingival scaling, SRP) decreases serum leukocytes (white blood cells) by 0.798 g/l (95% CL:0.717-0.879) relative to no treatment based on the 2 studies that had this endpoint and comparison. Teeuw et al, 2014 reported the outcomes of 25 clinical trials in 1748 patients and found that periodontal therapy (OHI, supragingival scaling, SRP) decreases serum CRP (C-reactive protein) by weighted mean difference of 0.50 mg/l (95% CL:0.22-0.78) relative to no treatment.[31] They also found that that periodontal therapy (OHI, supragingival scaling, SRP) decreases IL-6 (0.48 ng/L, 95% CL:0.06-0.90) , TNF-a (0.75 pg/L, 95% CL:0.17-1.34), and Fibrinogen (0.47 g/L. 95% CL:0.17-0.76). Orlandi et al, 2014 reported the outcomes of 3 clinical trials and found that periodontal therapy (OHI, supragingival scaling, SRP) improves flow mediated dilatation (FMD) by weighted mean difference of 6.64 (95% CL:2.83-10.44) relative to no treatment.[32] Changal et al, 2019 reported the outcomes of 6 clinical trials and found that periodontal therapy (OHI, supragingival scaling, SRP) decreases endothelial adhesion molecules (e-selectin) by standardized mean difference of 0.52 mg/l (95% CL:0.10-0.94) relative to no treatment.[33] These studies collectively support that control of local periodontal inflammation through periodontal therapy decreases the presence of systemic inflammatory biomarkers and mediators (CRP, IL-6, fibrinogen, e-selectin), as well as improving physical measures of cardiovascular health (FMD – flow mediated dilatation).

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[40] as defined by guidelines for the 2017 World Workshop of Periodontology.[39] 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.[40]

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.[42] 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[43,44] the latter of which are associated with the initialization of the inflammatory processes involved in periodontal disease.[45-50] Samples of plaque from subgingival areas in subjects brushing with stannous fluoride dentifrice have been shown to exhibit decreased virulence ex vivo.[51,52] 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.[53] 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 cardiovascular disease. Patients with periodontal disease are at higher risk for cardiovascular disease, putatively because of the impact of local chronic periodontal inflammation leading to an increase in systemic inflammatory mediators in the vascular system. The patient and dental professional must work together to stop this vicious 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 cardiovascular disease patients can be improved by increased education on the requirements for elevated oral hygiene and also the selection and application of selective oral products applied to their personal hygiene. The causative factors for gingivitis in cardiovascular 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 cardiovascular disease patients in maintaining their oral health.

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