

Chun, Yong-Hee P. Chun, Kyoung-Ryul J. Olguin, De'Avlin, Wang, Hom-Lay. Biological foundation for periodontitis as a potential risk factor for atherosclerosis. [Review] J Periodontal Res 2005; 40:87-95, February 2005. (123 Refs)

Purpose: The aim of this paper is to review the current understanding about the molecular biological interactions between periodontal disease and atherosclerosis and the biological possibility of periodontitis as a potential risk factor for cardiovascular disease.

Materials and Methods: Literature review and search of Medline and PubMed databases.

Findings and Conclusions: The Framingham Heart Study was a landmark study in the 1960s which listed classical risk factors for CHD and atherosclerosis, however these were not sufficient to account for the multifactorial nature of the pathological nature of these diseases. Consequently several risk factors have been identified which include microbial pathogens, non-specific markers for low-grade inflammation, fibrinogen, C-reactive protein, leukocyte count and antibodies to heat-shock proteins. The possible niches from which these spread are the bronchii, GI tract, pharynx and the periodontium. However inconsistencies in statistical associations between pathogens such as *H. pylori*, *C. pneumoniae*, cytomegalovirus and arteromatous plaques may suggest that these pathogens may be coincidental rather than associated with the pathology. *P. gingivalis* has been recognized as a key pathogen and risk factor for periodontal disease. Most significant among its virulence factors is its ability to invade epithelial cells, connective tissue as well as endothelial cells. The invasion is mediated through upregulation of adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), P and E selectins, only in the presence of fimbriae. *P. gingivalis* lipopolysaccharides trigger inflammatory pathways through cytokine production (TNF, IL-1, PgE2). Endothelial cell damage has been shown to be promoted by the ability of *P. gingivalis* to adhere, invade and proliferate in coronary endothelial cells. This is believed to interfere with the dilatory function of the vessel through damage of the endothelial and smooth muscle cells. Cytokines have been identified in the arteromatous plaque to regulate recruitment of monocytes, low density lipoproteins, smooth muscle cell proliferation and hemostatic factors. The release of cytokines from macrophages and other cells is thought to be triggered by bacterial components leading to systemic activation of phagocytic cells. PgE2, IL1 β , and TNF- α derived from periodontitis helps to further recruit more inflammatory cells which may result in higher counts of cholesterol laden macrophages called foam cells. The macrophages thus transformed into foam cells stimulate the production of proinflammatory cytokines, leading to endothelial dysfunction. T-cell response further contributes to foam cell production and smooth muscle formation. T-cells and antibodies may recognize binding sites shared by host and infectious organisms heat shock proteins. This resulting immunological cross reaction may result in cell damage and proliferation of smooth muscle cells thereby perpetuating atherosclerotic plaque formation. CRP is linked to atherogenesis

through proliferation of cytokines such as IL-1, IL-6, TNF- α , and interferon- γ . Binding of LDL and formation of foam cells is also mediated by CRP. Destabilization of preexisting atherosclerotic plaques occurs in the presence of vascular stenosis. Oral bacteria stimulate platelet aggregation and thrombus-like formation. MMP's derived from macrophages weaken the fibrous cap of the atheroma, promoting plaque rupture. Periodontal pathogens are known to induce MMP's and hence might contribute to plaque rupture.

Yamazaki K, Honda T, Oda T et al. Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine levels in Japanese periodontitis patients. J Periodont Res 2005;40:53-58.

Purpose: A pilot study to determine whether the presence of chronic periodontitis and periodontal treatment could influence serum levels of CRP, IL-6 and TNF- α in a Japanese population.

Materials and Methods: 24 treatment subjects (aged 20-59) with moderate to advanced periodontitis and 21 control subjects (aged 29-56) without periodontitis participated in this study. Clinical exam included plaque control record, probing depths, attachment levels and alveolar bone resorption. Treatments group had ScR, followed with surgical procedures as needed. Patients were followed monthly or every 3 months depends on individual patient's needs. Serum samples were taken from treatment group, 3 months after completion of active therapy. CRP (hs-CRP) were measured with nephelometry, a latex particle-enhanced immunoassay; IL-6 and TNF- α were determined with sensitive enzyme linked immunosorbent assay.

Findings and Conclusions: Periodontal status demonstrated a significant improvement in all patients following treatment. The difference in hsCRP level between patients and control subjects demonstrated a trend toward higher level in patient at baseline. This difference decline following treatment, and this decline was not statistically significant. IL-6 and TNF- α had no change following periodontal treatment. This study failed to demonstrate that periodontal disease significantly affects serum levels of systemic inflammatory markers of CRP, IL-6 and TNF- α . Large scale studies are needed to determine the impact of periodontitis on systemic inflammation.

Weiss OI, Caton J, Blieden T, Fisher SG, et al. Effect of the Interleukin-1 genotype on outcomes of regenerative periodontal therapy with bone replacement grafts. J Periodontol 2004;75:1335-1342. (43 Refs)

Purpose: To investigate the effect of the IL-1 genotype on treatment outcomes of regenerative periodontal therapy with bone replacement grafts.

Materials and Methods: In this retrospective study 44 subjects, 23 males and 21 females ages 28-30 were selected. Inclusion criteria were: 1) patients who had undergone periodontal therapy with bone replacement grafts 2) Caucasians and Hispanic and 3) patient who had adequate documentation of WMPI, WMBI (Whole mouth plaque and bleeding index), PD and CAL of sites treated with bone replacement grafts before therapy and for smoking status categorized as: never smoked, past smokers, light smokers (≤ 10 cigarettes per day) and heavy smokers (≥ 10 cigarettes per day). Only allografts, xenografts or alloplasts were included in the study. IL-1B genotyping was performed to detect allele 2 at the IL-1B and IL-1A loci. A subject was considered IL-1 genotype positive if he/she had at least one "allele 2" in each of the loci. Data was analyzed using the non-parametric Wilcoxon rank sum test and multivariate linear regression models were fitted to determine effect on PD and CAL.

Findings and Conclusions:

1. In this study population, 29.55% (13) were IL-1 genotype positive.
 2. There were no light smokers in the IL-1 genotype positive group.
 3. The genotype positive subjects had a smaller PD reduction than genotype-negative subjects, but this difference was statistically insignificant.
 4. The genotype-positive subjects had more mean clinical attachment gain than the genotype-negative subjects but this was also insignificant.
 5. The only significant variables to influence the clinical parameters were the pre-surgical PD and plaque index scores.
 6. In the study, the deeper the probing depths at baseline, the greater the reduction in PD and the greater the attachment gain after surgical treatment with bone replacement grafts.
 7. The higher the pre-surgical plaque index, the less clinical attachment gain.
- The IL-1 genotype status of the subjects did not significantly influence the clinical treatment outcomes of regenerative periodontal therapy with bone replacement grafts.

Trackman PC, Kantarci A. Connective tissue metabolism and gingival overgrowth. Crit Rev Oral Biol Med 2004;15: 165-75.

Purpose: To discuss drug-induced gingival overgrowth and its pathogenesis.

Materials and Methods: Author opinion and lit review.

Findings and Conclusions: Gingival overgrowth lesions all contain fibrotic or expanded connective tissues with various levels of inflammation and an enlarged gingival epithelium. The degrees of inflammation, fibrosis, and cellularity depend on the duration, dose, and identity of the drug, on the quality of oral hygiene, and on individual susceptibility that stems from genetic factors and environmental influences. While the incidence of this side-effect can be as high as 65% in epileptics, 70% in transplant patients, and 30% in hypertension subjects, variation exists in the reported prevalence and severity of the clinical problem. Clinical and histological characteristics of drug-induced gingival overgrowth include hyperplasia in junctional epithelium and hypertrophy in keratinized epithelium and excessive connective tissue accumulation. Dose-dependent correlations with the severity of gingival overgrowth are weak, but decreased drug use in general results in reduced severity of gingival pathology. Age, gender, concomitant medication with multiple drugs, local factors such as plaque accumulation, and genetic disposition are additional complicating risk factors in drug-induced gingival overgrowth. Therapy of drug-induced gingival overgrowth would seem to be most simply accomplished by the use of alternate medications that do not induce gingival overgrowth, and new medications are under development. At this time, however, older medications are still in active use. Treatment of the gingival overgrowth lesion itself can be complicated due to the superimposed inflammation on the fibrotic tissue enlargement. Traditionally, periodontal therapy offers removal of the inflammatory component of the overgrowth through scaling and gingival curettage, followed by excision of the overgrown gingiva. For patients with severe gingival overgrowth and who require continuous drug therapy for medical reasons, gingivectomy must be repeated periodically due to the recurrent nature of drug-induced gingival overgrowth. Cyclosporin A was found to increase glycosaminoglycan secretion by fibroblasts, and nifedipine and phenytoin increased heparan levels. These drugs inhibit gingival fibroblast extracellular matrix production and/or cell proliferation. Direct regulation of extracellular matrix metabolism or proliferation of gingival fibroblasts by these drugs is probably not the primary mechanism responsible for gingival overgrowth. Deregulated cytokine balances may contribute more significantly to the development and maintenance of gingival overgrowth. cyclosporin A, and nifedipine increase production of fibroblast cytokines and prostaglandin E₂ although lymphocytes and macrophages may be important sources of these factors. Collagen turnover is unusually high in periodontal tissues. Wound healing and connective tissue turnover are largely controlled by chemokines and cytokines secreted by inflammatory cells such as macrophages and lymphocytes and, to a lesser degree, by fibroblasts. Proliferation and differentiation of connective tissue cells and production of extracellular matrix are controlled by cytokines that initiate signaling cascades mediated by specific receptors. In addition, extracellular matrix elements interact with cell-surface receptors, including integrins, that initiate or modulate signaling cascades. Recent studies

demonstrate abnormally high levels of specific cytokines in gingival overgrowth tissues. This suggests that substances that cause gingival overgrowth may do so by altering the normal balance of cytokines in gingival tissues. Cytokines and growth factors found at elevated levels in human drug-induced gingival overgrowth include interleukin-6 (IL-6), IL-1 β , platelet-derived growth factor-B (PDGF-B), fibroblast growth factor-2 (FGF-2), transforming growth factor- β (TGF- β), and connective tissue growth factor (CTGF). Phenytoin, cyclosporin A, and nifedipine gingival overgrowth tissues contain subpopulations of macrophages and other inflammatory cells that differ from those in healthy control gingival tissues. A reduction in the number of Langerhans cells in nifedipine and cyclosporin A gingival overgrowth occurs and suggests a modification of an inflammatory reaction that influences the level of helper T-lymphocytes and cytokine profiles. Inflammatory cell populations that are altered as a result of drug therapy are likely to modify the gingival tissue response. CTGF is found to occur at elevated levels in a variety of fibrotic pathologies. Recent studies indicate that CTGF binds to other growth factors, resulting in either inhibition or stimulation of their activity. The hypothesis regarding the role of CTGF in gingival overgrowth was that TGF- β 1 might induce CTGF, which in turn would stimulate extracellular matrix production in gingival fibroblasts. CTGF is rapidly and potently up-regulated by TGF- β 1, and that CTGF stimulates insoluble collagen accumulation in human gingival fibroblast cultures. It is present at elevated levels in phenytoin- and nifedipine-induced gingival overgrowth tissues, but not in cyclosporin-A-stimulated gingival overgrowth. The more fibrotic tissues appear to contain the highest levels of CTGF. This supports the notion that cyclosporin-A-induced gingival overgrowth tissues are significantly more inflamed and less fibrotic than phenytoin- or nifedipine-induced gingival overgrowth. It is surprising that CTGF is elevated in phenytoin-induced gingival overgrowth tissues. PGE₂ is a potent and rapid down-regulator of CTGF. Phenytoin stimulates prostaglandin E₂ (PGE₂) production by gingival fibroblasts, and it is well-known that human gingival tissues accumulate significant levels of prostaglandins including PGE₂. The fact that CTGF is elevated in phenytoin-induced gingival overgrowth tissues, therefore, is unexpected and raises the notion that human gingival tissues may be metabolically unique in their response to PGE₂. A major and serious side-effect of cyclosporin A therapy is kidney fibrosis, which can result in kidney failure. Cyclosporin A stimulates levels of circulating TGF- β in vivo, and enhances TGF- β production by renal cells and lymphocytes. This results in increased collagenous extracellular matrix synthesis and deposition in the glomeruli of the kidney, as demonstrated by studies with anti-TGF- β 1 antibodies that block renal fibrosis and renal dysfunction. Taken together, these studies suggest that cyclosporin A stimulates TGF- β production that, in turn, leads to kidney fibrosis and nephropathy. Based on these findings, it seemed reasonable to expect that TGF- β 1 and its downstream target CTGF would be expressed at high levels in cyclosporin-induced gingival overgrowth. Contrary to these expectations, cyclosporin-induced gingival overgrowth tissues are highly inflamed, do not express high levels of TGF- β or CTGF and are not the most fibrotic tissues. These findings are surprising and indicate that oral bacteria and gingival cells and tissues must interact in unique ways in subjects receiving cyclosporin A that results in relatively greater inflammation and cellularity compared with other forms of gingival overgrowth. Connective tissue turnover in gingival tissues is

high, and destruction of the extracellular matrix occurs as a result of elaboration of extracellular proteinases, reduced MMP activity, and by phagocytosis and intracellular destruction of extracellular matrix components by lysosomal enzymes. phenytoin and cyclosporin A inhibit production of the lysosomal proteinase cathepsin L, but not cathepsin B, by human gingival fibroblasts. Cyclosporin may also inhibit phagocytosis of type I collagen. humans lacking lysosomal enzymes as a result of the rare genetic disease I-cell disease or mucopolysaccharidosis also have gingival overgrowth. inhibition of phagocytosis or of lysosomal enzymes appears likely to be a mechanism that could contribute to gingival overgrowth. gingival fibroblasts from individuals with inherited gingival overgrowth have an autocrine pathway involving high production of TGF- β coupled to a robust response to this factor, resulting in increased production of connective tissue cells and extracellular matrix. Genetic linkage studies of large families have identified more than one locus related to gingival overgrowth in hereditary gingival fibromatosis. Fibroblast heterogeneity and variations in the distribution of fibroblasts with different phenotypes have been suggested to contribute to drug-induced and inherited forms of gingival overgrowth. The presence of myofibroblasts in gingival overgrowth tissues has been reported, and these are highly differentiated cells that have a strong synthetic phenotype. A reduced rate of apoptosis is reported to contribute to the accumulation of gingival fibroblasts, perhaps with a greater synthetic or proliferative phenotype in nifedipine-induced gingival overgrowth. Not all forms of gingival overgrowth are the same, and more than one biological mechanism is likely to result in gingival overgrowth.

Scannapieco FA, Bush RB, Paju S. Association between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systemic review. Annals Periodontol 2003;9:38-53.

Purpose: To assess the association between chronic inflammatory periodontal disease and atherosclerosis, CVD, and stroke.

Materials and Methods: Literature review

Findings and Conclusions: Literature search resulted in 31 studies that examined the association of periodontal disease to CVD, stroke, or peripheral vascular disease. 4 of 5 case control studies reported positive association between indicators of poor dental health and outcomes of CVD. 11/15 cross sectional studies support a modest association of periodontal disease with CVD. 4 other studies have shown a positive association between periodontal disease and stroke, 1 shown association with peripheral vascular disease. In addition, several other studies demonstrate elevated CRP, fibrinogen, WBC, cholesterol, and cytokines in association with periodontal disease. Limitations of this analysis are absence of standard definition and measure of periodontal disease that complicate interpretation of results. The association between atherosclerosis-induced disease and periodontal disease is due to etiologic factors common to both disease processes. Periodontal disease appears to have moderate association with atherosclerosis-induced diseases, MI, and CVD. Insufficient evidence is available to support that periodontal intervention can prevent onset/progression of atherosclerosis-induced disease. Additional large scale longitudinal and intervention studies are needed to establish causality and validate the association.

Ruggiero SL, Mehrotra B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004; 62:527-534.

Purpose: To investigate the possibility of a relationship between osteonecrosis of the jaws associated with the use of bisphosphonates through a retrospective study.

Materials and Methods: A chart review was performed on 63 (45 females and 18 males) oncology patients who presented with a diagnosis of osteonecrosis or osteomyelitis of the jaw. Patients who had a prior history of radiation therapy to the jaw region or neoplastic disease that directly involved the jaws were excluded from the review.

Findings and Conclusions: Twenty-four patients (38%) presented with maxillary bone involvement (19 unilateral and 5 bilateral) and 40 (63%) had mandibular bone involvement (37 unilateral and 3 bilateral). Patient 15 presented with exposed and necrotic bone in all 4 quadrants. The typical presenting symptoms were pain and exposed bone at the site of a previous tooth extraction. However, 9 of the 63 patients (14%) had had no history of a recent dentoalveolar procedure and nevertheless presented with spontaneous exposure and necrosis of the alveolar bone. Radiographs routinely showed regions of mottled bone, consistent with sequestrum formation. Chronic maxillary sinusitis secondary to necrotic bone and an oroantral fistula were evident in several patients with posterior maxillary involvement. On microscopic examination, all of the specimens consisted of necrotic bone with associated bacterial debris and granulation tissue. Culture results consistently revealed normal oral flora. Six patients had radiographic signs of osteolysis before the extraction of teeth, which suggested involvement of the alveolar bone before extraction. Biopsy of these lesions showed no evidence of metastatic disease. The majority of these patients required surgical procedures to remove the involved bone. The cessation of bisphosphonate treatment has not had a major impact on the progression of this process. Five patients had persistent bone necrosis and even developed new regions of exposed bone despite being removed from bisphosphonate therapy by their oncologists. Because of the current trend of increasing and widespread use of chronic bisphosphonate therapy, this observation of an associated risk of osteonecrosis of the jaw should alert practitioners to monitor for this potential complication. An early diagnosis might prevent or reduce the morbidity resulting from advanced destructive lesions of the jaw bone.

Renvert S and Persson R. Supportive periodontal therapy. Periodontol 2000;36:179-95.

Purpose: literature review.

Materials and Methods: review of articles assessing the overall efficacy of supportive periodontal therapy CSAD. Studies with a minimum duration of 36 months were included in this review.

Findings and Conclusions: Untreated chronic periodontitis has been described as a slowly progressive disease affecting individual teeth or tooth sites, showing evidence of periods of stability and periods of progression. At untreated sites, clinical measures of oral hygiene, gingivitis, pocket probing depths, and clinical attachment levels were poor predictors of disease activity over 18 months. Reddy's et al study demonstrated that 75% of untreated sites experienced no progression of disease or improved in the absence of care. Standard care of patients with previously untreated chronic periodontitis cases includes oral hygiene instructions and mechanical nonsurgical debridement. One of the treatment objectives has been to reduce probing pocket depths. This treatment phase is referred to as Initial Cause Related Therapy (ICRT). The therapeutic goals of SPT are:

- to prevent the recurrence and progression of periodontal disease in patients who have been previously treated for gingivitis, periodontitis, and peri-implantitis.
- To prevent the incidence of tooth loss by monitoring the dentition and any prosthetic replacement of natural teeth.
- To increase the probability of locating and treating in a timely manner.

The initial results obtained following ICRT could not be sustained using standardized SPT (3-6 month intervals) over 3 years. A slight increase in pocket probing depth and loss of attachment over time as well as loss of teeth are reported. The data reported in this review imply that SPT programs should be individualized in accordance with the patient's risk profile. The importance of good to excellent oral hygiene to obtain a reliable and successful outcome of periodontal therapy has been identified in many studies. Professionally delivered and frequently repeated supragingival toothcleaning in combination with self-performed plaque control, has a significant effect on the subgingival microbiota of moderate to deep periodontal pockets.

Frequency of supportive maintenance care: the rationale for 3 month recall intervals for SPT is most likely based on published studies that used 3-4 month intervals as part of study design rather than a result of studies comparing the efficacy and safety of different time intervals. The frequent maintenance care is necessary to eliminate/reduce subgingival proportions of pathogens associated with periodontitis. However, several other studies have demonstrated that longer intervals between maintenance care visits can effectively prevent further disease progression. Few studies have compared the impact of different recall intervals. However, Rosen et al studied the effects of 3,6,12, and 18- month intervals between supportive recall treatments. With the exception of a trend of some rebounding sites >6mm and attachment loss at molar sites with furcation invasion in the 18-month recall group, no differences were found between the groups. The results of this study suggest that recall intervals could be extended to at least 1

year in subjects with a history of limited susceptibility to periodontitis. Compliance with supportive periodontal recall visits: studies that have assessed the level of patient compliance considering both acceptable levels of oral hygiene and attendance to scheduled regular maintenance care visits. Studies have assessed compliance with attendance only during the last 3 years suggest that the attendance compliance varies between 26 to 77%. Other studies suggest that female patients are more compliant than men. Two other studies showed that older patients are more compliant than younger patients, whereas another study suggested the opposite. SPT with adjunct use of antimicrobials/antibiotics: antimicrobials have been used to compensate for inadequate mechanical oral hygiene. They can be administered using different delivery systems (dentifrices, solutions for oral rinses or flushing of the periodontal pockets). There are few long-term studies suggesting the efficacy of such antimicrobials in SPT programs. A number of short-term studies (12 months or less) imply that antibiotics are effective adjuncts to ICRT and that the effect may be sustained over a longer period of time.

Maintenance care of patients with dental implants: the long-term success of implants has been reported in a large volume of studies. However, infections (peri-implantitis) occur in about 4-19% of implants. Few studies exist on the long-term efficacy of treatment of peri-implantitis. A 3 year follow up study of implants treated with autogenous bone suggested that initial improvements can be stabilized. In a 5-year case report study by Leonhardt et al. it was found that in spite of antibiotic retreatment for the reoccurrence of peri-implantitis, four of nine individuals demonstrated implant loss during the follow-up period. Limited data exist on the long-term effects of SPT of dental implants. It seems reasonable to anticipate that the long-term success of dental implants can be achieved using the same principles as used for the maintenance of teeth in patients with a past history of periodontitis.

Complications of supportive periodontal therapy:

Caries: few studies have specifically addressed root caries as a complication during a period of SPT. However, studies suggest that the prevalence of root caries in periodontally treated patients is very high. Intact root cementum prevents dentin caries, and one of the consequences of periodontal therapy is the removal of root cementum. Data suggested an association between the level of oral hygiene and the number of root surface lesions and likewise an association with salivary *Streptococcus mutans* counts.

Endodontic lesions: approximately 30% of all extractions of teeth over a 4-year period of SPT are the consequence of peri-apical lesions.

Periodontal abscesses: appears to occur in approximately 35% of subjects on SPT.

Root sensitivity: it is well established that following ICRT, root sensitivity is common, especially if treatment involves surgical procedures. In most cases such sensitivity decreases over time. Reports on root sensitivity during SPT vary from 15% to 98% and are often associated with root surface exposure and gingival recession.

Risk assessment for recurrence of disease in patients with a history of periodontitis: many studies have shown that the predictive value of routine periodontal parameters is relatively low. Bleeding on probing cannot be used as a predictor of periodontal disease progression. However, it is at approximately 25% or less of sites a good predictor of stable conditions. Smoking on the hand represents a true risk factor for periodontitis. Data suggest that genetic factors

may explain approximately 50% of all cases of periodontitis. A genetic marker has recently become available to determine a polymorphism genotype of patients who may be more susceptible for chronic periodontitis. Prospective studies have shown that interleukin (IL)-1 gene positive non-smoking subjects over the age of 50 have significantly deeper periodontal pocket probing than their IL-1 negative gene counterparts.

Multifactorial risk diagram: to define SPT intervals and procedures, the risk for further periodontitis progression can be assessed using a combination of risk factors in a multifactorial risk diagram. The number of risk factors can vary in the presented diagram of six vectors:

- Proportion of sites with BOP
- Number of sites with a pocket probing depth >5mm
- Number of missing teeth
- Proportion of mesial/distal sites showing evidence of a distance CEJ to bone level >4mm on radiographs
- Genetic factors
- Smoking status with regard to pack/year.

As a result of this review, a standardized SPT program cannot be recommended. However, categorizing the patients into risk profiles may be a useful strategy to assess appropriate and individualized SPT time intervals and procedures.

Rahman A, Rashid S, Noon R et al. Prospective evaluation of the systemic inflammatory marker C-reactive protein in patients with end-stage periodontitis getting teeth replaced with dental implants: a pilot investigation. Clin Oral Implant Res;2005;16;128-34.

Purpose: The purpose of this study was to evaluate if dental implants placed after extraction in patients with end-stage periodontitis affect the serum CRP levels.

Materials and Methods: 10 patients six of whom were males and four females between the ages of 54-74 with advanced chronic periodontitis were selected as participants for this study. All patients had CRP levels above 1mg/dl and a minimum of 10 teeth. Patients received a preoperative dose of 2 gm of amoxicillin prior to the surgery. The surgery was performed under I.V sedation during which all infected teeth were extracted and the extraction sockets curetted to remove granulation tissue. At least five implants were placed in each patient. Post operatively all patients received 500 mg of amoxicillin t.i.d for 7 days and 400 mg ibuprofen t.i.d prn pain. Patients were also instructed to rinse with a Chlorhexidine mouth wash for 30 days. No systemic antibiotics or NSAIDS were administered to the patients subsequent to the post operative dose for 12 months after surgery. Peripheral blood was examined for CRP levels prior to surgery and at approximately 3 month intervals for 12 months.

Findings and Conclusions: The average CRP level before extraction and dental implant placement was 3.45 mg/dl and this decreased over 12 months to 1.55 mg/dl. The preoperative and three month values were not statistically different but a significant difference was observed from the later collection periods. It was observed that the actual CRP levels decreased for 6 months post operatively and then stabilized. This study therefore concluded that extraction of advanced periodontally compromised teeth and their replacement with dental implants lead to a decrease in the CRP levels and that dental implant placement did not change the lowered CRP levels.

Montebugnoli L, Servidio D, Miaton RA, et al. Periodontal health improves systemic inflammatory and haemostatic status in subjects with coronary heart disease. J Clin Periodontol 2005; 32:188-92. (41 Refs)

Purpose: To assess whether intensive dental care may produce a periodontal improvement in patients with proved CHD along with a change in a series of systemic inflammatory and haemostatic factors related to CHD.

Materials and Methods: 20 non-smoking males (10 had never smoked, the remaining quit at last 2 months before entering the study), aged 40-45 years (mean 49.6±4.5) with proven CHD were studied. At the initial exam, all patients were checked clinically and radiologically (panoramic tomography), with two dental indices; CPSS (Clinical periodontal sum score) and CRSS (Clinical and radiographic sum score). Blood samples were also taken. After a 4-month period, all subjects were reassessed as non-treatment control, and then, all subjects underwent a non-surgical periodontal treatment. After 3 months of completion of treatment (Treatment period), all subjects were re-examined in the same fashion, and all collected data were statistically analyzed.

Findings and Conclusions: Finally, 18 subjects completed the study. No significant difference in any of the dental indices and the systemic inflammatory and haemostatic factors were detected at the control (non-treatment) period with respect to base line. After the treatment period, both oral indices showed a significant decrease ($F=14.1$, $p<0.01$ for CPSS; $F=15.3$, $p<0.01$ for CRSS). All systemic inflammatory indices also decreased after the treatment period, but only the decrease in CRP and Ox-LDL reached statistical significance ($F=3.22$, $p<0.05$ for CRP; $F=5.18$, $p<0.01$ for Ox-LDL). Non-surgical periodontal therapy seems to affect systemic markers of inflammation and haemostasis and could have the potential to influence cardiovascular diseases.

Grau AJ, Becher H, Zeigler CM, Dorfer CE. Periodontal disease as a risk factor for ischemic stroke. Stroke 2004; 35:496-501. (23 Refs)

Purpose: To investigate whether periodontal disease is independently associated with acute ischemic stroke or transient ischemic attack in general and with its etiologic subtypes.

Materials and Methods: 303 hospitalized patients with acute cerebral ischemia (experimental group), 300 population controls, and 168 hospital controls (control group) were studied (age: range from 18 to 75 years old). All subjects were interviewed with standardized questionnaire focused on medical, dental, and social history, and habits such as smoking and drinking. Experimental group were classified into stroke subtypes with established criteria, and they were examined within 3.3 ± 2.2 days after ischemia. CAL was used for assessment of periodontitis, and was classified into 5 grades as follows, absence, mild periodontitis (defined as mean CAL < 3 mm), 3-4.5 mm, 4.5-6.0 mm, and severe periodontitis (defined as mean CAL > 6 mm). Gingivitis severity was assessed with the Löe and Silness Gingival Index. Severe gingivitis was defined as index values > 1.2, and dental plaque was graded according to the Silness and Löe Plaque Index. DMFT Index was also used for caries assessment. Radiographic bone loss was measured from CEJ to the most apical extension of defect with panoramic radiographs. All obtained variables were statistically analyzed.

Findings and Conclusions: The mean CAL was higher, indicating more severe periodontitis in experimental group than in both control groups. Similar results were found for number of teeth, gingivitis, radiological bone loss, and plaque index. Increasing severity of periodontitis was associated with an increasing risk of cerebral ischemia. Severe periodontitis increased the risk by a factor of 4.3 (Odds ratio). In contrast, missing teeth, plaque index, and caries were not independent risk factors. Periodontitis represented a risk factor in men and younger subjects but not in women or older individuals (60 years). Regarding etiologic subgroups, severe periodontitis was an independent risk factor for atherothrombotic, cryptogenic, and cardioembolic origins. In analysis, severe radiological bone loss and severity of gingivitis were significantly associated with cerebral ischemia. When statistically tested together with periodontitis, severe gingivitis even appeared as the more important risk factor. This study concluded that periodontal disease was significantly associated with cerebral ischemia.

Gonzalez-Moles MA, Scully C. Vesiculo-erosive oral mucosal disease-management with topical corticosteroids: (1) fundamental principles and specific agents available. J Dent Res 2005, 84(4): 294-01.

Purpose: To set out the key aspects of the use of topical corticosteroids in oral medicine.

Materials and Methods: Lit review & author's opinion.

Findings and Conclusions: Immunologically mediated diseases that affect the oral mucosa present with inflammation and loss of epithelial integrity, through cellular and/or humoral immunity-mediated attack on epithelial connective tissue targets. The main clinical features are ulceration and reddening, with pain that can be severe and debilitating. In many patients, these lesions are chronic and/or present a marked tendency to recur, and often significantly interfere with such basic activities as eating, drinking, talking, and maintaining normal social relationships.

Corticosteroids play a central role in treatment of vesiculo-erosive lesions. However, the frequency and severity of the adverse effects associated with the use of systemic corticosteroids have led to the increased use of the use TC. Corticosteroids can:

- 1) Reduce the emigration of leukocyte and exudation of plasma constituents.
- 2) Maintain the integrity of cell membranes
- 3) Inhibit the release of lysozmes from granulocytes and phagocytosis
- 4) Inhibit fibroblast proliferation, suppressing fibrosis.

The main oral mucosal conditions that are amenable to treatment with topical steroids (TC) are listed in table 1.

Table 1. Candidate Oral Erosive Lesions for Treatment with Topical Corticosteroids

- Recurrent aphthous ulcers
- Oral manifestations of Behçet's disease, Reiter's syndrome, acute vulvar ulcer, MAGIC syndrome, PFAPA syndrome, ulcerative colitis, Crohn's disease, Melkersson-Rosenthal syndrome, Sweet's syndrome, among others
- Drug-induced ulcerations mediated by an immune mechanism
- Lichen planus
- Cicatricial pemphigoid
- Mucous membrane pemphigoid
- Bullous pemphigoid^a
- Erythema multiforme
- Linear IgA dermatosis
- Pemphigus vulgaris^a

TC should be applied only in cases that onset with exclusively oral lesions and low titers of circulating antibodies. When a TC is prescribed, the basic rule is that a TC of a potency appropriate to the severity of the clinical symptoms should be used, at the lowest possible

concentration and frequency compatible with maintaining the effectiveness of the treatment. The specific diagnosis, the severity of oral disease, the presence or absence of extra-oral lesions, and the medical history of the patients are the key factors that determine the selection of a topical or systemic treatment.

Table 2. Common Formulations Used for the Application of the Most Widely Used Topical Corticosteroids in Oral Medicine

Corticosteroid	Concentration	No. Applic./Day	Applic. Time	References
Clobetasol propionate	0.05%	2–3 applic./day	5 min	Lozada-Nur <i>et al.</i> , 1991, 1994; Lozada-Nur and Miranda, 1997; González-Moles <i>et al.</i> , 2002b,c, 2003
Fluocinonide	0.05%	5–10 applic./day	5 min	Voute <i>et al.</i> , 1993; Lozada-Nur <i>et al.</i> , 1994; Carbone <i>et al.</i> , 1999
Triamcinolone acetonide	0.1%–0.2%	10 applic./day	5 min	Vincent <i>et al.</i> , 1990; Lozada-Nur <i>et al.</i> , 1991; Lozada-Nur and Miranda, 1997

The success of a topical medicine depends on the drug being in contact with the lesion for an appropriate time. Two main factors are involved. The first is the number of applications per day. When high potency corticosteroids are used, two or three daily applications are generally prescribed. A second factor that decisively affects the duration of the drug lesion contact is the vehicle used for the specific TC formulation. TCs known to be used in oral medicine can be classified broadly as having mild, moderate, high, or very high potency. Mild-potency steroids, they are generally considered appropriate for the treatment of clinically unimportant autoimmune disease of the oral mucosa such as hydrocortisone find favor in some patients with minor aphthous.

High-potency steroids: Clobetasol 17-propionate is currently the most widely used potent topical corticosteroid. It induces vasoconstriction, followed by reduction of the inflammation, presumably due to an alteration of histamine levels and to the effects of the catecholamines on peripheral blood vessels. Clobetasol propionate has showed a greater and faster remission of pain and other symptoms compared to fluocinonide.

Frachon X, Pommereuil M. et al. Management options for dental extraction in hemophiliacs: A study of 55 extractions (2000-2002). Oral Surg Oral Med Oral Pathol Radiol Endo 2005;99:270-5.

Purpose: to assess the efficacy of a protocol involving general patient preparation in conjunction with a local hemostasis technique combining a biological glue, a collagen-based alveolar packing material, absorbable sutures, and the use of an antifibrinolytic agent in conjunction with intermittent compression.

Materials and Methods: the study involved 55 extractions in 16 patients over a period of 2 years (May 2000 to May 2002). The patient distribution was:

- 6 cases of severe hemophilia A (13 extractions).
- 1 case of severe hemophilia A with inhibitors. (4 extractions).
- 1 case of moderate hemophilia A. (14 extractions)
- 4 cases of mild hemophilia A. (8 extractions).
- 1 case of moderate hemophilia B (13 extractions).
- 2 cases of mild hemophilia B. (3 extractions).

The protocol involved:

- Anesthesia: local anesthesia with articaine with epinephrine.
- Systemic treatment: Replacement therapy: with a recombinant factor VIII concentrate, 50 IU/kg was initiated in 6 out of 7 patients with severe hemophilia A and 1 patient with moderate hemophilia A.
All of the hemophilic B patients received a recombinant factor IX injection, 70 IU/kg.
Factor VIIa, 120 IU/kg was administered to 1 patient with severe hemophilia A with inhibitor.
Treatment with DDAVP was performed in 4 mild hemophilia A patients.
In all cases, the injection was administered 1 hour before surgery and a hemostasis assessment was carried out immediately before extraction.
- Local hemostasis: the same local hemostasis protocol was used for all patients:
 1. following thorough cleansing of the alveolus, insertion of biological glue.
 2. followed by insertion into the alveolus of gelatin packing.
 3. packing covered with a layer of biological glue.
 4. suturing with absorbable sutures, without attempting to totally seal the alveolus.
 5. finally, the sutures were covered with a layer of biological glue.

Following local hemostasis, intermittent compression (IAC) with tranexamic acid was prescribed.

Findings and Conclusions: 6 patients returned with postsurgical bleeding: 1 out of 2 patients with severe hemophilia A with inhibitor, 4 out of 6 patients with severe hemophilia A, 1 out of 3 observations with moderate hemophilia A, 1 out of 3 observations with moderate hemophilia B. One severe hemophilia A patient with inhibitor, presented with intrasinus bleeding on day 6 in the alveolus of the

maxillary molar. One patient presenting with severe hemophilia A, bled copiously from one of the extraction sites on day 5. One patient with severe hemophilia A presented with mild bleeding from a primary tooth extraction site of day 4. One patient with moderate hemophilia B, bled on day 8 from a primary extraction socket. No general complication was noted. At each time, bleeding concerned one extraction socket. No unusual bleeding was noted in any mild hemophilia patients.

A combination of an injection of coagulation factor concentrate or DDAVP, and use of an effective local hemostatic technique can, in most cases, prevent the onset of excessive, postsurgical bleeding. The combination of an intermittent tranexamic acid compression technique carried out by the patient in the days immediately following the surgical procedure can reduce the hospitalization duration to 1 day in most cases, and enhance comfort compared with compression splints.

Duarte PM, de Assis DR, Casati MZ et al. Alendronate may protect against increased periodontitis-related bone loss in estrogen-deficient rats. J Periodontol 2004;75:1196-1202.

Purpose: To evaluate the impact of alendronate (ALD) and estrogen (EST) therapies and their withdrawal on bone loss in experimental periodontitis in ovariectomized rats.

Materials and Methods: 87 Wistar rats were divided into 6 groups of 14-15 each. Group 1: sham surgery, ovaries intact, group 2: ovariectomy, group 3: ovariectomy with ALD treatment for 80 days, group 4: ovariectomy with 40 days of ALD treatment, group 5: ovariectomy with 80 days of EST treatment, group 6: ovariectomy with 40 days of EST treatment. 21 days after surgery, one lower molar was to receive a ligature to induce experimental periodontitis; the contralateral tooth was left unligated to serve as control. 60 days later, these rats were sacrificed and the periodontal specimens were prepared in paraffin sections with H&E staining. Area of bone loss in furcation region was graded histometrically by the point counting technique.

Findings and Conclusions: EST deficiency affected alveolar bone regardless of plaque accumulation and increased bone loss as a result of periodontitis. The continuous EST/ALD and interrupted ALD treatment were protective against EST deficiency on alveolar bone. Increased bone loss for EST deficient, EST continuous, EST withdrawal groups. The continuous/withdrawal ALD treatment reduced the impact of estrogen deficiency while EST continuous use did not. ALD treatment may offer protection against the impact of estrogen deficiency and has a significant residual effect after its withdrawal. Estrogen replacement therapy failed to offer such protection from bone loss.

D'Aiuto F, Ready D, Tonetti MS. Periodontal disease and C-reactive protein-associated cardiovascular risk. J Periodont Res 2004; 39:236-41.

Purpose: This study was carried out in healthy individuals to analyze the effects of periodontal therapy on changes in the CRP-associated CVD risk defined in AHA (American Heart Association) consensus conference.

Materials and Methods: Systemically healthy 94 patients with severe generalized periodontitis were selected. At baseline and at 2 and at 6 months after completion of non-surgical periodontal therapy, their periodontal parameters such as probing depths, recession, clinical attachment level, bleeding on probing, plaque score, microbial pathogens, and medical parameters were recorded, and their blood samples were also drawn. These periodontal parameters, and IL-6 and CRP from blood sample of each stage were monitored and analyzed statistically. Other potential parameters such as age, gender, ethnicity, BMI, and smoking were also calculated.

Findings and Conclusions: According to the AHA/CDC guidelines (based on the serum CRP levels), the patients were categorized to 3 groups, such as 12 in low, 47 in medium, and 35 in the high risk at baseline. The patients presenting with more widespread periodontitis (expressed by the presence of greater than median number of periodontal pockets 5mm or deeper) were in high-risk category compared to the low and medium. Age and BMI were also significant factors.

After 6 months of non-surgical periodontal therapy, significant improvement of periodontal parameters such as reduction of the number of pockets greater than 4mm, reduction in bleeding, plaque score, and periodontal pathogens was presented. Serum concentration of both CRP and IL-6 was also significantly reduced (31% and 12%, respectively). The reduction in numbers of subjects in the high and medium CVD risk classes was observed, 13 patients moved from the high to the medium, 25 from the medium to the low, and 2 from the high to the low. The patients who responded better to treatment were 4 times more likely to reduce their risk category. Extraction of hopeless teeth also contributed the reduction of risk category.

This study indicated the relationship between periodontitis especially severe one and CRP-associated CVD risk, and also showed non-surgical periodontal therapy would reduce the risk significantly. However, more well-defined and controlled clinical trial would be required.

Czerniuk MR, Gorska R, Filipiak K, Opolski G. Inflammatory response to acute coronary syndrome in patients with coexistent periodontal disease. J Periodontol 2004;75;1020-1026.

Purpose: The aim of this study was to evaluate the influence of periodontal disease on the inflammatory response measured by changes in the serum concentration of IL-1 and TNF- α in patients with acute coronary syndrome and coexistent periodontal disease.

Materials and Methods: The study evaluated 50 patients with the mean age of 51 years, who were admitted to the Coronary Care Unit of the University of Warsaw in Poland for complaints of chest pains and an initial diagnosis of acute coronary syndrome. 78 % of these patients were smokers since 18 years of age and smoked 20 cigarettes a day. Two patients were diabetic. Blood samples were taken from all patients to evaluate the levels of serum IL-1 and TNF- α . Examinations were carried out on day 1, 10-12 days following hospitalization, after 3 months and after 6 months of hospitalization. The second part of the examination was to verify initial diagnosis of chronic generalized periodontitis. Probing depths, Clinical attachment loss, level of root furcation and tooth mobility were measured. The simplified plaque index and bleeding index were measured. Each of the four parameters was evaluated on a scale of 1 to 4 points. The points from each parameter were then added and used to determine the extent of periodontal disease (lowest possible score = 4 points and highest score = 16 points). The fifty patients were divided into two groups based on their score. Group – I, ≤ 9 points (less advanced) and Group – II, > 10 points (more advanced). Patients were also divided upon the basis of attachment loss. Group III, CAL ≤ 3 mm and Group IV, CAL > 4 mm.

Findings and Conclusions: The study showed that for the group of 50 individuals with acute coronary syndrome and coexisting periodontal disease the mean PI was 72 % in females and 42 % in males and the BI was 86% in females and 78% in males. The study showed a non-significant raised mean IL-1 β concentration in group 2 compared to group 1. The maximum concentration was attained 3 months after the acute coronary syndrome and a sudden decrease to its lowest value in the sixth month. Similar IL-1 levels were seen in group 3 and 4. The study also showed a higher mean value for TNF- α concentrations in examinations 2, 3 and 4.