Periodontal disease elevates cholesterol, blood sugar, and crp

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Periodontal diseases—a modifiable source of systemic inflammation for the end-stage renal disease patient on haemodialysis therapy?

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Periodontal diseases—biology, pathology and clinical presentation

Periodontal diseases are a group of inflammatory diseases that affect the supporting tissues of the dentition. The most prevalent periodontal diseases result from the interaction of specific bacterial species with components of the host immune response in disease susceptible individuals and are currently classified as plaque-induced gingival diseases, early onset, chronic adult and aggressive periodontitis [1]. Plaque-induced gingival diseases are limited to the gingivae (gingivitis) and are characterized by erythema, oedema, haemorrhage and enlargement of the gingival tissues. Plaque- induced gingivitis is nearly pandemic in children and young adults and is reversible with treatment. In contrast, early onset, chronic and aggressive periodontitis are irreversible forms of periodontal disease that culminate in tooth loss if left untreated. Estimates of the prevalence of periodontitis vary with the clinical criteria used to define disease status; however, the Third National Health and Nutrition Survey (NHANES III) reported a 14% prevalence of moderate to severe periodontitis in the United States population >20 years of age [2].

The inflammatory lesion in periodontitis extends from the gingiva to include deeper connective tissues resulting in the loss of periodontal ligament and alveolar bone largely through the increased synthesis and activation of host-derived matrix metalloproteinases associated with the inflammatory response. Gingival epithelium migrates into the area of periodontal ligament and alveolar bone destruction, creating an ulcerated periodontal pocket around the affected tooth. The formation of a periodontal pocket is a characteristic feature of periodontitis in primates. Recruited into the connective tissue adjacent to the periodontal pocket is an intense cellular infiltrate consisting of polymorphonuclear leucocytes, monocytes/macrophages, B and T cell lymphocytes [3]. It has been estimated that, in an individual with moderate to severe periodontitis, the total surface area of the inflamed periodontal pockets can range from 8 to 20 cm^2 depending upon the number of teeth affected [4]. Therefore, the large surface area of the aggregate periodontal lesion can potentially become a significant source of inflammation in individuals with moderate to severe periodontitis.

The periodontal pocket is colonized by bacteria that exist in a stratified, highly ordered ecosystem, termed a dental biofilm or plaque, consisting of bacteria, bacterial products such as endotoxin/LPS and an extracellular matrix of polysaccharides, proteins and inorganic compounds.

The organization of the dental biofilm optimizes bacterial cell proliferation, while providing protection from host defence mechanisms as well as externally applied anti-microbials. Considerable variation has been reported in the profile of bacterial species present in subgingival plaque samples from individuals within a population and from sites within individuals. However, discreet complexes of bacterial species have been described in association with periodontal disease status and progression [5]. Plaque samples from periodontally healthy subjects consist largely of Gram-positive aerobic species. A shift towards increasing numbers of Gram-negative species, including the appearance of *Fusobacterium nucleatum* and various *Treponema* species, occurs in samples from subjects with plaque-induced gingivitis. The shift towards Gram-negative bacteria increases in plaque samples from subjects with chronic periodontitis with nearly 85% of the bacterial species reported as Gram-negative anaerobic or facultative anaerobic species including *Actinobacillus actinomycetemcomitans* serotypes a and b, *Campylobacter rectus, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythensis* and *Treponema denticola*. In particular, *P. gingivalis, T. forsythensis* and *T. denticola* have been associated with the progressing plaque front in chronic periodontitis [6].
However, colonization with a specific periodontal pathogen appears necessary but not sufficient for periodontal disease progression, since the majority of sites colonized remain quiescent for extended periods of time. Prospective studies in periodontally diseased populations have reported only 1%–2% of sites monitored over a 2-month period having lost >2 mm of attachment [7]. In addition, subjects with active periodontitis may be more immunologically responsive than those with quiescent disease. During progression of the periodontal lesion, the host may be exposed to increased antigenic challenge in sites with active extracellular matrix destruction since serum IgG antibody to *P. gingivalis* in particular has been reported to be elevated in subjects with periodontitis and further elevated with disease progression [8]. Therefore, when assessing the literature for possible contributions to systemic inflammation from periodontal diseases, it may be insufficient to dichotomize subjects as periodontally healthy or diseased but rather necessary to rank subjects according to disease severity and to distinguish between subjects with quiescent periodontitis from those whose disease has progressed.

Periodontal diseases—systemic inflammatory response and chronic kidney disease

Several studies have reported periodontitis to be associated with increased systemic inflammatory burden mediated perhaps through an acute phase response. An analysis of the NHANES III data found a positive association between C-reactive protein (CRP) values and periodontal disease severity [9], a finding that was later supported by results of the MI Life Study of New York [10]. Other cross-sectional studies have reported periodontitis to be associated with elevated CRP [11–13] as well as other serum components of the acute phase response including decreased high-density lipoprotein [11,12], increased low-density lipoprotein [12,13], increased blood glucose [12,14] and decreased peripheral blood neutrophil function [15] and count [16].
Two reports suggest that periodontitis may contribute to systemic inflammatory burden in end-stage renal disease (ESRD) patients on haemodialysis maintenance therapy. Levels of IgG antibody to *P. gingivalis*, but not to five other periodontal pathogens, correlated with elevated (>10 mg/l) CRP values in serum samples of 86 consecutive dentate haemodialysis patients in the United States. Also associated with elevated CRP were lower levels of haemoglobin, iron, transferrin saturation, albumin, total cholesterol and triglycerides. Serum IgG antibody remained significantly associated with CRP after controlling for non-periodontal sources of elevated CRP as well as haemoglobin, transferrin saturation and triglyceride values [17]. A recent report of 253 ESRD patients on haemodialysis maintenance therapy from Taiwan found age, smoking status, diabetes, dialysis vintage, decreased serum albumin, BUN and increased CRP values associated with increasing severity of periodontitis. When the data were analysed by multiple regression analysis, age, diabetes, smoking, albumin and dialysis vintage were found independently

associated with periodontitis severity. In addition, the authors reported the prevalence and severity of periodontitis to be greater than that of the general population [18], a finding also reported in two studies from the United States [19,20]. An increased prevalence of periodontitis was not found in a recent report from the Netherlands [21], however the study's sample size (a total of 42 chronic kidney disease patients of which only 28 were on haemodialysis) was not as large as the previously cited studies. Alternatively, this report may suggest that the presence of confounding variables, such as geographic differences in medical or dental care or ethnicity/race, exist in different ESRD populations.

Interestingly, several reports suggest that effective periodontal therapy may decrease systemic markers of inflammation. Periodontal therapy consisting of local root surface debridement and microbial plaque control was reported to decrease haptoglobin values for subjects with periodontitis, while the addition of flurbiprofen, a non-steroidal anti-inflammatory drug, in conjunction with periodontal therapy was reported to decrease both haptoglobin and CRP values [22]. Two recent studies reported decreases in both interleukin-6 (IL-6) and CRP 6 months after initial periodontal therapy alone. These effects were greatest for those subjects with the most favourable response to periodontal therapy, as measured by clinical indices, and remained significant after correction for age, gender, body mass index and smoking status [23,24]. Taken together, these studies suggest that not only can periodontitis elevate CRP and other systemic markers of inflammation but effective periodontal therapy may decrease CRP values.

The above reports are of significance for the ESRD patient population, since elevation in serum inflammatory markers such as CRP have been reported to be robust predictors of both all-cause and cardiovascular mortality in this population [25]. Undoubtedly, many sources of inflammation exist for ESRD patients on haemodialysis therapy but in view of the incidence of periodontitis in the general population and possible increased incidence and severity in the ESRD population, periodontitis may be one source of systemic inflammation that can be readily managed through effective periodontal therapy.

The clinical management of periodontitis

A primary objective of initial periodontal therapy is to alter the subgingival bacterial profile from one associated with disease (Gram-negative facultative or anaerobic bacteria) to one associated with health (Gram-positive aerobic bacteria). An additional objective is to decontaminate root surfaces that have been exposed to pathogenic bacteria within the periodontal pocket of necrotic, calcified bacterial plaque deposits (dental calculus) and absorbed bacterial products, including LPS and endotoxin. Current approaches for initial periodontal therapy include meticulous oral hygiene procedures performed daily by the patient to remove newly formed subgingival plaque in an attempt to alter the subgingival bacterial profile coupled with professional local mechanical root debridement ('root planning') to remove calculus and absorbed bacterial products [26]. Adjunctive attempts to alter the host response to subgingival Gram-negative bacteria have also shown promise. For example, the combination of initial periodontal therapy with the administration of matrix metalloproteinase inhibitors, such as low-dose doxycycline, has shown additional efficacy over mechanical debridement alone [27]. The anticipated result of initial periodontal therapy is the resolution of gingival inflammation and the reattachment of gingival tissues to the root surface, resulting in the reduction of periodontal pocket depth to a level maintainable by the patient through daily oral hygiene procedures. However, the presence of extensive pocket formation associated with severe osseous defects or exposure of anatomical features such as root furcations may inhibit attempts at effective oral hygiene or local root debridement. Therefore, for patients who have not resolved after initial periodontal therapy and who demonstrate adequate levels of plaque control, surgical pocket elimination, either by resection or regeneration, may be

indicated. Severe periodontal pocket formation not amendable to surgical intervention will ultimately result in loss of the affected tooth.

The ESRD patient on haemodialysis maintenance therapy with periodontitis is medically complex and presents the dental practitioner with several challenges in the management of their periodontal condition. Accordingly, close communication between the patient's dentist and nephrologist is essential to optimize periodontal management. Overviews on the dental management of the ESRD patient on haemodialysis maintenance have been published [28,29]; therefore, only major management issues will be summarized here. Since invasive dental procedures, including root planning and extractions, can result in transient bacteraemia, antibiotic prophylaxis prior to the dental appointment according to the American Heart Association Guidelines has been recommended to protect vascular access sites [29]. Anaemia and possible clotting deficiencies should be evaluated in consultation with the patient's physician, and dental appointments should be scheduled the day after haemodialysis [28]. Due to the high prevalence of hypertension in the ESRD population, care should be used with local anaesthetics containing vasoconstrictors, and the dosage and administration of drugs cleared by the kidneys altered with respect to decreased or absent kidney function [30]. Finally, it has been suggested that osseous periodontal surgical procedures such as bone grafting or dental implants may be contraindicated in patients with significant renal osteodystrophy [31].

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Conclusions

Moderate to severe periodontitis is prevalent in the general population and may be more prevalent in the ESRD population on haemodialysis maintenance therapy. Periodontitis has been associated with increased markers of systemic inflammation, including elevated CRP, and limited studies in the general population suggest that effective periodontal therapy may decrease CRP levels. Therefore, periodontitis in ESRD populations may be a covert source of systemic inflammation that can be managed through effective periodontal therapy. However, whether treatment of moderate to severe periodontitis in ESRD populations will result in decreased CRP levels and, more importantly, decreased incidence of atherosclerotic complications awaits the results of interceptive clinical trials in this population.

Conflict of interest statement. None declared.

(See related article by Borawski *et al*. The periodontal status of pre-dialysis chronic kidney disease and maintenance dialysis patients. *Nephrol Dial Transplant* 2007; 22: 457–464.)

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Protective effects of grape seed proanthocyanidins against oxidative stress induced by lipopolysaccharides of periodontopathogens.

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BACKGROUND: During phagocytosis or stimulation with bacterial components, macrophages activate various cell processes, including the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are critical for successful defense against invading organisms. Increased levels of ROS/RNS create oxidative stress that results in tissue and bone destruction. Grape seed proanthocyanidins have been reported to possess a wide range of biologic properties against oxidative stress. In the present study, we investigated the effects of a grape seed proanthocyanidin extract (GSE) and commercial polyphenols on the production of ROS and RNS and on the protein expression of inducible nitric oxide synthase (iNOS) by murine macrophages stimulated with lipopolysaccharides (LPS) of periodontopathogens. METHODS: Macrophages (RAW 264.7) were treated with non-toxic concentrations of either GSE or commercial polyphenols (gallic acid [GA] and [-]-epigallocatechin-3-gallate [EGCG]) and stimulated with LPS of Actinobacillus actinomycetemcomitans or Fusobacterium nucleatum, and iNOS expression was evaluated by immunoblotting. Nitric oxide (NO) production was quantified using the colorimetric Griess assay, whereas ROS production was measured with the fluorescent 123-dihydrorhodamine dye. RESULTS: GSE strongly decreased NO and ROS production and iNOS expression by LPS-stimulated macrophages. GA also revealed a strong inhibitory effect on NO production without affecting iNOS

expression but slightly increasing ROS production. EGCG showed an inhibitory effect on NO and ROS production and on iNOS expression by macrophages. CONCLUSION: Our findings demonstrate that proanthocyanidins have potent antioxidant properties and should be considered a potential agent in the prevention of periodontal diseases.

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