The incidence of end-stage renal disease (ESRD) is increasing and patients receiving renal replacement therapy including hemodialysis, peritoneal dialysis or renal transplantation will comprise an enlarging segment of the dental patient population. Renal replacement therapy can affect periodontal tissues including gingival hyperplasia in immune suppressed renal transplantation patients and increased levels of plaque, calculus and gingival inflammation and possible increased prevalence and severity of destructive periodontal diseases in ESRD patients on dialysis maintenance therapy. Also, the presence of undiagnosed periodontitis may have significant effects on the medical management of the ESRD patient. Periodontitis has been found to contribute to systemic inflammatory burden including the elevation of C-reactive protein (CRP) in the general population. Atherosclerotic complications including myocardial infarction and stroke are the primary causes of mortality in the ESRD population and, in contrast to that of the general population, the best predictor of all cause and cardiac death in this population is CRP. Consequently, periodontitis may be a covert but treatable source of systemic inflammation in the ESRD population. The objective of this review was to explore the interaction between chronic renal disease, renal replacement therapy and periodontal disease on the basis of results of studies published within the last decade.

Chronic renal disease, end-stage renal disease and renal replacement therapy

The kidneys perform four essential functions: excretion of the end products of metabolism, particularly urea, regulation of blood volume and electrolyte concentration, regulation of erythrocyte production in the bone marrow through the secretion of erythropoietin and participation in calcium homeostasis through hydroxylation of vitamin D3 into active or inactive metabolites (Fogo and Kon, 2004). Therefore, any pathologic process that results in decreased renal function would be expected to have serious, pleiotrophic effects. Renal function is assessed, in part, by measurement of the glomerular filtration rate (GFR). GFR is estimated using serum creatinine concentration and several other patient variables by the following equation (Levey et al, 2006):

\[
GFR(\text{ml min}^{-1}/\text{1.73 m}^{2}) = 175 \times (S_{CR})^{-1.154} \times (\text{age in years})^{0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African–American})
\]

Glomerular filtration rate in the normal adult varies between 100 and 120 ml min\(^{-1}\)/1.73 m\(^2\) body surface.
area. With the functional loss of renal glomeruli caused by glomerular or renal interstitial disease, kidney function decreases. As expected, in view of the functions performed by the kidney, a major clinical consequence of chronic renal disease is the retention of a large number (>90) of compounds, many of which are toxic that are normally excreted by the kidney, collectively called the uremic syndrome (Vanholder et al., 2003). Also observed are disturbances in blood electrolyte and acid-base balance (including hyperkalemia and acidosis), anemia, renal osteodystrophy (because of hypocalcemia, hyperphosphatemia and resultant hyperparathyroidism), hypertension, and in the young, delay in growth largely because of secretion of insulin-like growth factor I (Riegden, 2003). Early in chronic renal disease, several compensatory mechanisms and intervention strategies can maintain homeostasis including glomerular hyperfiltration and hypertrophy of the remaining glomeruli, alteration in the diet and the use of phosphorous binding compounds, administration of 1, 25 dihydroxy vitamin D3, recombinant erythropoietin and anti-hypertensive medications, and in the young, growth hormone administration (Davidovich et al., 2005). However, once the GFR falls below the range of 10–20 ml min⁻¹/1.73 m² body surface area in progressive chronic renal disease and blood urea nitrogen levels rise to 100–150 mg dl⁻¹ (normal values are between 10 and 20 mg dl⁻¹), compensatory mechanisms fail and ESRD ensues (Riegden, 2003; Vanholder et al., 2003; Fogo and Kon, 2004).

The most common causes for ESRD in the United States are diabetes mellitus, glomerulonephritis and chronic hypertension (US Renal Data System, 2005). The incidence of new ESRD cases in the United States in 2003 (the most recent year these data were available) was 352.7 cases per million individuals. The point prevalence of ESRD in the United States has been increasing with reported rates of 923.5, 957.6, 990.7, and 1550.0 cases per million individuals for the years 2000–2003, respectively (US Renal Data System, 2005). The increased prevalence of ESRD is largely attributed to the increasing prevalence of chronic diseases such as type II diabetes mellitus. The main cause of death in ESRD populations on renal replacement therapy is athero sclerotic complications including myocardial infarction (Paparello et al., 2002; US Renal Data System, 2005). The high prevalence of diabetes mellitus, altered lipoprotein metabolism and hypertension undoubtedly contribute to increased cardiovascular risk observed in the ESRD population. However, inflammation is also a major contributing factor as the best predictor of both cardiac and all-cause mortality in ESRD populations is C-reactive protein (CRP) (Yeun et al., 2000), a major acute phase protein and systemic marker of inflammation (Lacson and Levin, 2004).

End stage renal disease is fatal without renal replacement therapy, which can be provided by dialysis, either HD or peritoneal dialysis (PD), or by renal transplantation (Riegden, 2003). In HD, urea and other low molecular weight molecules diffuse during exchange from the patient’s blood across an extracorporal filtering/dialysis membrane into an electrolyte and pH balanced dialysis solution. HD sessions typically last 3–5 h and are usually required three times per week. Vascular access is most commonly achieved via puncture using wide bore needles into a surgically created arteriovenous fistulae usually sited in the forearm and clotting is inhibited by heparin. HD is by far the more common form of dialysis in adult ESRD populations with a point prevalence rate of 1021.1 cases per million individuals reported for 2003 in the United States (US Renal Data System, 2005).

In contrast to the synthetic dialysis membranes used in HD, PD uses the tissues lining the patient’s peritoneal cavity to dialyze urea and other small molecular weight compounds from the blood. PD employs a surgically placed catheter to access the patient’s peritoneal cavity that is intermittently infused and then drained with a sterile dialysis solution. PD can either be performed throughout the day (continuous ambulatory PD or CAPD) or overnight using an automated machine (automated continuous cyclic PD). PD is less restrictive on the patient’s time by obviating the need for travel three times a week to a dialysis unit for therapy but presents the additional risk of difficult-to-manage peritoneal infections. However, at best, both forms of dialysis are able to provide approximately 10% of the renal function provided by two normally functioning kidneys and none of the kidney’s endocrine functions. Therefore, the ESRD patient on dialysis maintenance therapy remains in a continued state of chronic renal failure.

Far greater renal function can be provided by renal transplantation, the preferred form of renal replacement therapy. Success is dependent upon closely matching the donor and recipient ABO blood type and major histocompatibility leukocyte antigen (HLA) complex (Seikaly et al., 2001). Because of the near impossibility of achieving a perfect HLA complex match between a non-consanguineous donor and recipient, continuous immune suppression after renal transplantation is required to prevent graft rejection. This is usually provided by the combination of corticosteroids, calcineurin inhibitors such as cyclosporine A or tacrolimus to suppress IL-2 production and lymphocyte proliferation inhibitors such as azathioprim or mycophenolate mofetil. Graft survival rates of 83% for 1 year and 65% for 5 years have been reported for cadaver-donor kidney transplants and improved rates of survival of about 10–15% have been reported for live-donor kidney transplants (Seikaly et al., 2001). The disadvantages of renal transplantation include susceptibility to opportunistic infection because of immune suppression, a tendency for decreased kidney function with increasing age of the transplanted kidney and hypertension (Seikaly et al., 2001).

Effects of chronic renal disease on periodontal tissues

Chronic renal disease has well-documented effects on oral tissues including xerostomia, delayed tooth eruption, calcifications leading to obliteration of pulp...
chamber and canals, enamel hypoplasia, decreased caries rates and altered salivary pH levels (reviewed in Davidovich et al, 2005; Proctor et al, 2005). In addition, dental management has to be modified for the renal dialysis patient to account for possible prolonged bleeding, alteration in drug administration because of decreased GFR, loss of low molecular weight compounds through dialysis, and antibiotic prophylaxis to protect vascular access sites (reviewed in Kerr, 2001; Little et al, 2002). Specific effects of chronic renal disease and renal replacement therapy on periodontal tissues include gingival hyperplasia in immune suppressed renal transplantation patients and increased levels of plaque, calculus and gingival inflammation and possible increased prevalence and severity of destructive periodontal diseases in ESRD patients on dialysis maintenance therapy.

Gingival hyperplasia secondary to calcineurin inhibitors and calcium channel blockers is the most reported effect of chronic renal disease on periodontal tissues. Gingival overgrowth with these drugs can be severe and treatment frequently requires surgical resection. In recent reports, the prevalence of cyclosporine-induced gingival hyperplasia for renal transplant patients varied from 22% to 58% (Somacarrera et al, 1994; Ellis et al, 2004; Spolidorio et al, 2006). Most studies report gingival hyperplasia to be associated with increased cyclosporine dosage, the presence of increased plaque and gingival inflammation and is more commonly seen in the young (Somacarrera et al, 1994; Ellis et al, 2004). Improved oral hygiene has been reported to decrease the incidence or delay the onset of gingival hyperplasia (Somacarrera et al, 1994; Ellis et al, 2004). In the past 10 years, tacrolimus has been increasingly favored over cyclosporine as an immune suppressive drug, especially in younger renal transplant recipients. The incidence of gingival hyperplasia in renal transplant patients receiving tacrolimus is typically less than those reported for cyclosporine, generally between 0% and 15% (Ellis et al, 2004; Spolidorio et al, 2006). In addition, some reports suggest cyclosporine-induced gingival hyperplasia can be decreased without surgical intervention by substitution with tacrolimus (Hernandez et al, 2003). However, for both cyclosporine and tacrolimus, the addition of a calcium channel blocker, especially nifedipine, can increase the incidence and severity of gingival hyperplasia (Ellis et al, 2004; Spolidorio et al, 2006). The mechanism of calcineurin inhibitor induced gingival hyperplasia is not known and certainly not all renal transplant patients exhibit gingival hyperplasia. Of interest, a recent report examined the association among two functional polymorphisms in the transforming growth factor-β1 (TGF-β1) gene, serum levels of TGF-β1 and the prevalence and severity of gingival hyperplasia in renal transplantation patients receiving both cyclosporine A and calcium channel blockers. Polymorphisms that produced the highest levels of serum TGF-β1 also had the highest incidence of gingival hyperplasia, suggesting a genetic basis for susceptibility to cyclosporine-induced gingival hyperplasia and the possible involvement of TGF-β1 in the mechanism of cyclosporine-induced gingival overgrowth (Radwan-Oczko et al, 2006).

Most recent studies focusing on the periodontal health of ESRD patients on HD maintenance therapy have reported the presence of poor oral hygiene and attendant gingival inflammation. Increased levels of plaque have been reported for HD populations from several countries including Brazil (Souza et al, 2005), Canada (Klassen and Krasko, 2002), Jordan (Al-Wahadni and Al-Omari, 2003), Israel (Davidovich et al, 2005), Spain (Gavalda et al, 1999; Castillo et al, 2006), Taiwan (Chen et al, 2006), Turkey (Duran and Erdemir, 2004), and the United States (Naugle et al, 1998). Associated with increased plaque in ESRD populations on HD maintenance therapy was increased calculus formation (Gavalda et al, 1999; Klassen and Krasko, 2002; Al-Wahadni and Al-Omari, 2003; Duran and Erdemir, 2004; Davidovich et al, 2005; Souza et al, 2005; Bots et al, 2006; Chen et al, 2006) and attendant gingival inflammation (Naugle et al, 1998; Gavalda et al, 1999; Klassen and Krasko, 2002; Al-Wahadni and Al-Omari, 2003; Duran and Erdemir, 2004; Davidovich et al, 2005; Souza et al, 2005; Chen et al, 2006).

Several possible reasons have been forwarded to account for the almost universally reported increased levels of plaque, calculus and gingival inflammation in renal HD populations. Most prominently, ESRD patients on HD are in a state of chronic kidney failure resulting in the uremic syndrome, and uremia has been associated with immune dysfunction including defects in lymphocyte and monocyte function (Cohen et al, 1997). Therefore, if uremia is responsible for the increased gingival inflammation observed in this population, increased dialysis vintage maintenance therapy should be associated with increased gingival inflammation and periodontitis incidence and severity. Increased gingival inflammation and periodontitis has been reported in association with increased dialysis vintage in several (Duran and Erdemir, 2004; Davidovich et al, 2005; Chen et al, 2006) but not all (Naugle et al, 1998; Al-Wahadni and Al-Omari, 2003; Marakoglu et al, 2003) studies. Of interest, one study directly assessed the effect of uremia on the gingival inflammatory response to increasing bacterial plaque load using the experimental gingivitis protocol of Loe. At 28 days after the cessation of oral hygiene, the authors reported no difference in gingival indices between a group of six HD patients and a group of six age and sex matched non-uremic controls (Kitsou et al, 2000).

In addition to uremia, the presence of confounding diseases such as diabetes mellitus could contribute to the increased gingival inflammation reported for renal HD populations, especially in view of the high incidence of diabetes mellitus in ESRD populations and the strong association between diabetes mellitus and periodontitis in the general population (Grossi et al, 1994). To test this possibility, Chuang and co-workers compared 43 diabetic with 85 non-diabetic ESRD patients on HD. Decreased salivary flow and pH was associated with increased caries rates in the diabetic group but no difference was reported for gingival inflammation or
periodontitis (Chuang et al., 2005). Alterations in calcium homeostasis leading to secondary hyperparathyroidism have been suggested as a possible cause of increased gingival inflammation and possible alveolar bone loss in renal HD populations. However, a single study of 35 ESRD patients on HD maintenance therapy with secondary hyperparathyroidism failed to find an association between parathyroid hormone level and alveolar bone loss or periodontal pocket depth when compared with 35 case matched non-ESRD controls (Frankenthal et al., 2002). Finally, it may be possible that the intense psychological and demands on personal time that ESRD places on HD patients may decrease the priority of seeking oral health care and maintaining good oral health. In support of this hypothesis, several studies have reported decreased utilization of dental care services in ESRD patient populations on HD (Nauge et al., 1998; Klassen and Krasko, 2002).

In view of the nearly universal reports of increased plaque, calculus and gingival inflammation, an increased incidence and severity of periodontitis would be expected in ESRD patient populations on HD maintenance therapy. However, conflicting results on the status and severity of periodontitis have been reported for ESRD populations. Using loss of attachment as a criterion for periodontitis, no increase in periodontitis was found in a study of 38 children in the United Kingdom, 11 of whom were receiving HD; however, enamel defects and gingival hyperplasia were reported (Nunn et al., 2000). A study of 36 adult ESRD patients receiving HD reported no increase in periodontitis when compared with a group of age and sex matched control subjects; however, the controls were drawn from a dental school periodontal clinic population who were presumably seeking periodontal care (Marakoglu et al., 2003). A recent study from Spain assessed the periodontal status of 52 ESRD patients receiving HD and found no increase in periodontal indices when compared with case-matched controls. The authors did note that the HD group had greater numbers of periodontopathic bacterial species than the control group (Castillo et al., 2006). Finally, a recent study from the Netherlands of 42 ESRD patients, 28 of whom were receiving HD, did not find an increased loss of attachment when compared with 42 healthy case-matched controls (Bots et al., 2006).

In contrast, a study of 65 chronic renal disease subjects, aged 2–27 years, of whom 22 were on HD maintenance therapy, reported increased attachment loss when compared with age-matched controls (Davidovich et al., 2005). A study of 128 adult ESRD patients on HD from Taiwan reported increased periodontal disease as measured by the Community Periodontal Index (Chuang et al., 2005). A study from Turkey of 342 ESRD patients on HD therapy found increased periodontitis as measured by the Community Periodontal Index of Treatment Needs (Duran and Erdemir, 2004), although measurement of attachment loss is not part of this index. A second study from Taiwan of 253 renal patients receiving HD reported increased rates of periodontitis when compared with national data on periodontal disease for the Taiwanese population. Of interest after multivariate analysis, the best predictors of periodontitis in this population were increased age, presence of diabetes mellitus, smoking, decreased serum albumin, and dialysis duration (Chen et al., 2006). We have reported in abstract form of increased prevalence and severity of periodontitis as measured by increased pocket depth and attachment loss in a study of over 150 ESRD patients on HD maintenance therapy when compared with the 7447 dentate subjects who received periodontal examinations in the Third National Health and Nutrition Survey (NHANES III). The subjects were drawn from dialysis units in New York City and North Carolina. A greater prevalence and severity of periodontitis was found in subjects from the New York City HD sites (Yoshino et al., 2005).

Although it cannot be concluded that periodontitis is more prevalent and severe in ESRD patients on HD maintenance therapy from the results of the above studies, it may be important to note that reports of positive associations examined larger renal HD populations. The inclusion of large numbers of subjects is critical in epidemiologic studies of populations that present with multiple potential confounding variables such as the medically complex ESRD population. Potential confounding variables in the ESRD population include: the high prevalence of diabetes mellitus, smoking, dialysis vintage, age, degree of medical management of renal failure complications, potential ethnic/racial or demographic variables that may influence access to dental care, potential recruitment bias (only periodontally healthy or better maintained patients may wish to participate), and the selection of appropriate control populations. However, no data exist to suggest that the prevalence in the ESRD population is less than the 14% prevalence of moderate to severe periodontitis reported for the general population (Brown et al., 1996) but may in fact be substantially greater. In light of the fact that all ESRD patients on HD maintenance therapy are potential renal transplant candidates and the possible contribution of periodontitis to the inflammatory burden in the ESRD population (discussed below), it appears important to assess and maintain the periodontal health of this at risk population.

**Potential effects of periodontitis on ESRD patients on hemodialysis maintenance therapy**

When compared with the general population, ESRD patients on HD maintenance therapy suffer a greatly increased rate of mortality because of atherosclerotic complications, especially among the younger age groups. The period prevalent rate of mortality for ESRD populations on HD in the United States was 231.5 cases per 1000 patients or 23% in 2003. Atherosclerotic complications including acute myocardial infarction, cardiac arrest, cardiac arrhythmia, and cerebral vascular disease accounted for 44% of all reported deaths for that year while infection was the second most common cause of mortality (US Renal Data System, 2005). Mortality is highly associated with
increased inflammatory burden in the ESRD population as CRP, an acute phase protein and systemic marker of inflammation, is a major risk predictor for both cardiac and all cause mortality in this population (Yeun et al, 2000). CRP has also been defined as a major risk predictor for atherosclerotic complications in the general population (Ridker et al, 1997, 2000; Cesari et al, 2003; Pearson et al, 2003; Pai et al, 2004) and supplements traditional cardiac risk factors such as serum lipoprotein profiles in the prediction of cardiac events (Ridker et al, 2002).

While it has become clear that inflammation is central to the pathogenesis of atherosclerosis (Ross, 1999; Libby, 2002) it is not clear whether elevated CRP levels merely reflect the inflammation present within an unstable or progressive atherosclerotic plaques or if elevated CRP from peripheral sources directly participates in the pathogenesis of atherosclerotic complications (Pearson et al, 2003). Although controversial, an increasing body of evidence has implicated CRP in the pathogenesis of atherosclerotic complications. CRP is a member of the pentraxin family of proteins present in all vertebrates thus far studied, and binds phosphoethanolamine and phosphocholine of cell membranes. When bound, CRP can activate the complement cascade (Lacson and Levin, 2004). Receptors for CRP are present on macrophages, monocytes, and neutrophils and therefore, bound CRP can also target both host and bacterial disrupted cell membranes for phagocytosis in a manner analogous to a true opsonin. However, CRP has been localized with complement in infarcted but not in non-infarcted myocardium of patients with fatal myocardial infarctions (Lagrand et al, 1997). CRP has also been shown to increase endothelial cell expression of VCAM-I ICAM-I, E-selectin (Pasceri et al, 2000) and monocyte chemoattractant protein (Pasceri et al, 2001). In addition, CRP has been shown to bind oxidized phospholipids to facilitate uptake by macrophages (Chang et al, 2002). Therefore, elevated CRP levels may lead to a more intense local CRP deposition and thus amplify subsequent inflammatory reactions leading to atherosclerotic complications. In support of this hypothesis, reduction in CRP levels using statin therapy has been shown to decrease the incidence of subsequent cardiac events (Ridker et al, 2005).

Moderate to severe periodontitis has been shown to increase serum inflammatory markers including CRP. An analysis of NHANES III found a positive association between CRP values and periodontal disease severity (Slade et al, 2000), a finding that was later supported by results of the MI Life Study of New York (Noack et al, 2001) and the 5552 subject Atherosclerosis Risk in Communities Study (ARIC) (Slade et al, 2003). A follow-up report from the ARIC study reported that initial or severe periodontitis was also associated with renal insufficiency, defined as a GFR of < 60 ml min⁻¹/1.73 m², and with increased serum creatinine levels (Kshirsagar et al, 2005). Other cross-sectional studies have reported periodontitis to be associated with elevated CRP as well as other serum components of the acute phase response including decreased high density lipoprotein (Buhlin et al, 2003; Craig et al, 2003), increased low density lipoprotein (Craig et al, 2003; Slade et al, 2003), increased blood glucose (Katz, 2001; Craig et al, 2003) and decreased peripheral blood neutrophil function (Fredriksson et al, 1999) and count (Loos et al, 2000). Most importantly, two intervention studies have reported that effective periodontal therapy can result in decreased levels of CRP in periodontitis patients (D’Aiuto et al, 2004, 2005). Whether effective periodontal therapy resulting in decreased CRP levels can translate into decreased incidence of cardiac events awaits the results of ongoing interventional studies.

Risk for atherosclerotic complications based on CRP in the general population have been published as < 1.0 mg l⁻¹ as low risk, between 1.0 and 3.0 mg l⁻¹ as average risk and > 3.0 mg l⁻¹ as high risk. A two fold greater risk of cardiac events is predicted in the high vs low risk groups (Pearson et al, 2003). As many factors contribute to inflammatory burden in ESRD populations including the type of dialysis membrane, vascular access sites, recurrent infections, malnutrition and uremia, the use of CRP cutoff values derived from the general population may need to be adjusted upward in the ESRD population (Lacson and Levin, 2004). But clearly, any intervention that can decrease systemic inflammatory burden could greatly benefit this population. Two reports suggest periodontitis may contribute to systemic inflammatory burden in ESRD populations. Levels of IgG antibody to Porphyromonas gingivalis, but not to five other periodontal pathogens, correlated with elevated (> 10 mg l⁻¹) CRP values in serum samples of 86 consecutive dentate HD patients in the United States. Also associated with elevated CRP were lower levels of hemoglobin, 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, hemoglobin, transferrin saturation and triglyceride values (Rahmati et al, 2002). A recent report of 253 ESRD patients on HD maintenance therapy from Taiwan clinically examined subjects for periodontal disease status and severity and reported CRP values to be correlated with periodontitis severity (Chen et al, 2006). As in the general population, whether effective periodontal therapy can decrease CRP levels and result in decreased risk for subsequent cardiac events remains to be tested in clinical intervention trials in the ESRD population.

Conclusions

Chronic renal disease can have significant effects on periodontal health including gingival hyperplasia in renal transplant patients receiving calcineurin inhibitors and calcium channel blockers. In addition, most epidemiologic studies have reported increased levels of plaque, calculus and gingival inflammation in ESRD populations. Whether an increased prevalence and severity of periodontitis exist in ESRD populations remains controversial. However, in view of the high rate...
of mortality from atherosclerotic complications, the strong association between increased inflammatory burden and atherosclerotic complications, and the possible contribution to systemic inflammation from periodontitis, the periodontal status of all chronic renal disease patients needs be carefully monitored.

References


