Periodontal Infections, Inflammatory Markers in Chronic Kidney Disease

Eric Sanjay Choudhury
University of Connecticut Health Center

Follow this and additional works at: https://opencommons.uconn.edu/sodm_masters
Part of the Dentistry Commons

Recommended Citation
https://opencommons.uconn.edu/sodm_masters/177
Periodontal Infections, Inflammatory Markers in Chronic Kidney Disease

Eric Sanjay Choudhury

DMD, University of Pennsylvania, 2006

A Thesis
Submitted in Partial Fulfillment of The
Requirements for the Degree of
Master of Dental Science
at the
University of Connecticut
2010
Master of Public Health Thesis

Periodontal Infections, Inflammatory Markers in Chronic Kidney Disease

Presented by

Eric Sanjay Choudhury

Major Advisor: Efthimia Ioannidou, DDS, MDSc

Associate Advisor: Anna Dongari-Bagtzoglou, DDS, PhD

Associate Advisor: Gian Pietro Schincaglia, DMD, PhD

Associate Advisor: Joseph Burleson, PhD

University of Connecticut

2010
Acknowledgments

This work could not have been possible without the invaluable help of the members of my advisory committee:

Dr. Effie Ioannidou: for her continued mentorship, motivation and scholarship
Dr. Anna Dongari-Bagtzoglou: for her deep insight and continued encouragement
Dr. Gian Pietro Schincaglia: for being a selfless and dedicated clinician and teacher
Dr. Joseph Burleson: for his valuable mentorship in biostatistics and research methods

I also thank the faculty at the Division of Periodontology, for they have helped me become a knowledgeable and capable member of this profession and specialty.

I also thank the National Institutes of Health and the General Clinical Research Center at The University of Connecticut Health Center for funding this research.
Dedication

I dedicate this work to my wife Alma, whose love, care and support made it possible for me to overcome hardships and pursue my goals.
# Table of Contents

**APPROVAL PAGE** ........................................................................................................... ii

**ACKNOWLEDGMENTS** ................................................................................................... iii

**DEDICATION** ................................................................................................................ iv

I. **GENERAL INTRODUCTION** ........................................................................................ 1
   A. **CHRONIC KIDNEY DISEASE: OVERVIEW AND CURRENT CONCEPTS** ............. 2
   B. **INFLAMMATION: ROLE IN CHRONIC KIDNEY DISEASE AND OUTCOMES** ........... 5
   C. **PERIODONTITIS: ASSOCIATION WITH SYSTEMIC INFLAMMATION** ...................... 6

II. **PERIODONTITIS IN CKD PATIENTS** ......................................................................... 9
   A. **OBJECTIVES** ........................................................................................................... 9
      1. Hypothesis: ............................................................................................................ 9
      2. Specific Objectives: ............................................................................................... 9
   B. **INTRODUCTION:** .................................................................................................. 10
   C. **MATERIALS & METHODS:** ............................................................................... 10
      1. Subject recruitment ............................................................................................... 11
      2. Data Collection .................................................................................................... 11
      3. Statistical analysis ............................................................................................... 13
   D. **RESULTS:** ............................................................................................................. 13
      1. Population characteristics .................................................................................... 13
      2. General periodontal findings .............................................................................. 13
I. General Introduction
A. **Chronic Kidney Disease: Overview and Current Concepts**

Chronic kidney disease (CKD) is a generalized term for a variety of chronic conditions that result in compromised kidney functions[1]. Under normal physiologic conditions, the kidneys serve several functions: regulation of fluid volume and the acid/base balance of plasma; excretion of nitrogenous waste; synthesis of erythropoietin, 1,25-dihydroxy-cholecalciferol, and renin; and different drug metabolism[2]. Kidney function is assessed by the glomerular filtration rate (GFR), which is estimated by the use of the following formula[3]:

\[
\text{GFR (mL/min per 1.73 m²)} = 186 \times (S_c)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female})
\times (1.210 \text{ if African-American}),
\]

where \( S_c \) is serum creatinine concentration in mg/dL, and age is in years.

Based on the estimated GFR, there are five stages of CKD[3] as presented in Table 1. CKD stage 5, known as End-Stage Renal Disease (ESRD), is defined by GFR <15 ml/min/1.73m² and characterized by bilateral, progressive, chronic deterioration of nephrons, which are the kidney functional units. The kidneys are no longer able to maintain normal homeostasis resulting in uremia caused by renal failure, retention of excretory products, and interference with endocrine and metabolic functions[4]. Stages 3 and 4 can also be characterized by uremia, but usually in lower levels than stage 5[5]. Stage 5 is caused by any condition that
could potentially destroy the nephrons, but the most common causes are diabetes mellitus, hypertension, and glomerulonephritis[6].

When the patient is diagnosed with CKD stage 5, the goals of treatment are to maintain quality of life, control disease progression and prevent further complications. At this stage, treatment focuses on dietary modification in an effort to decrease the retention of nitrogenous waste products and control fluid and electrolyte imbalances[7]. When conservative treatment fails and the number of functional nephrons is reduced to the point that the kidneys can no longer filter the blood and adequately remove nitrogen-containing compounds, either renal replacement therapy or renal transplantation is necessary[8].

Renal replacement therapy (dialysis) is a medical procedure that facilitates the removal of water and waste products such as creatinine and urea from the blood. More than 350,000 individuals receive dialysis in the United States at a cost of more than $7 billion per year[9]. The procedure can be accomplished by either peritoneal dialysis or hemodialysis. Peritoneal dialysis involves infusion of a hypertonic solution into the peritoneal cavity 4 to 5 times per day via a permanently placed peritoneal catheter[10].

The most common type of renal replacement therapy is hemodialysis therapy (HD), with approximately 90% of dialysis patients receiving this form of treatment[9]. HD treatments are performed every two or three days, usually
three or four hours each through vascular access connected to the hemodialysis
device. Vascular access is accomplished by a permanent and surgically-placed
arteriovenous (AV) fistula, a graft or a venous catheter. From 1996 to 2007, AV
fistula use rose from 24% to 47% among HD patients in the US[11]. Despite
being a life-saving technique, HD only provides about 15% nephron function[12]
and the 1-year survival rate is 78%, while the 5-year survival rate is 28%[13].
The procedure requires a substantial time commitment from the patient and
potential complications include potential infection of the fistula/graft site,
septicemia, infective endocarditis, cardiovascular disease, hypotension[14],
hypoxemia, and arrhythmias[15]. Renal transplantation is a long-term alternative
to dialysis, but in itself is also associated with a significant number of
complications such as cardiovascular complications[16] and increased
susceptibility to infection or malignancies[17] despite offering obvious
advantages such as elimination of dialysis time commitment, fewer diet and fluid
restrictions, and a better quality of life[12].

CKD is a major global health issue. It is estimated that up to 19 million
Americans have CKD and 350,000 are currently on dialysis[18]. Each year,
approximately 79,000 new cases of stage 5 CKD are diagnosed—a rate of 1.3 in
10,000 persons. Approximately 60,000 Americans die annually as a result of
stage 5 with cardiovascular disease being the main cause of mortality in this
population[19].
B. **Inflammation: Role in Chronic Kidney Disease and Outcomes**

Inflammation is the biological response of tissue to harmful stimuli such as pathogens or irritants[20]. Research has shown inflammation to be a common feature in patients suffering from CKD. 30-50% of dialysis patients showed evidence of an elevated inflammatory response as indicated by high levels of serum C-reactive protein (CRP) [21]. Other studies have found similar results in regards to CRP levels in ESRD patients[22-24].

Identifying the sources of inflammation in CKD patients is still under investigation. Evidence supports the idea that deterioration of renal function is associated with increased serum cytokine levels[25], while other studies showed that increased levels of advanced glycation end products due to decreased renal clearance are contributory factors to vascular inflammation [26]. Persistent infections such as *Chlamydia pneumoniae*[27, 28], clotted access grafts[29], and dental infections[30, 31] have also been suggested as possible sources of inflammatory responses in CKD patients.

Over the past decade, inflammation has been found to play a strong role in the pathogenesis of atherosclerosis in patients with ESRD[32] and associations between inflammation and endothelial dysfunction have been documented[21]. Inflammatory markers such as high sensitivity C-reactive protein (hsCRP) and
the pro-inflammatory cytokine interleukin-6 (IL-6) are elevated in ESRD patients with cardiovascular disease (CVD)[33]. CRP is a powerful risk predictor for the development of CVD[34-36], and this inflammatory burden has been suggested to be a significant contributor to the high CVD-induced mortality rate in dialysis patients[37].

In addition, inflammatory markers including serum CRP and IL-6 have been documented as strong predictors of HD poor outcome. Elevated CRP levels have been associated with increased mortality in both hemodialysis[35, 38, 39] and peritoneal dialysis patients[40], as well as otherwise healthy adults[41]. Elevated serum IL-6 levels have also been shown to predict myocardial infarction in non-renal patients, as well as mortality in the elderly[42, 43].

C. **Periodontitis: Association with Systemic Inflammation**

Periodontal diseases are chronic, predominantly Gram-negative infections of the oral cavity that are initiated in the gingiva and, if untreated, lead to alveolar bone destruction and eventual tooth loss[44, 45]. Collectively, periodontal diseases affect over 70 percent of the adult population[46].

During the past two decades, a field of periodontal research known as "periodontal medicine" has emerged[47], investigating the link between periodontal disease and other systemic diseases. Recent evidence suggests
that there may be an association between periodontal infections and several systemic conditions including diabetes, pneumonia, cardiovascular disease, and adverse pregnancy outcomes, although other investigators have found conflicting results.

For more than a century, clinical researchers have been investigating the biologic mechanism that could explain the link between periodontal infections and systemic inflammatory diseases. In 1900, Hunter proposed the “Focal Infection Theory,” which supports the role of bacterial by-products from a chronic, localized infection that could be disseminated throughout the body and cause disease in other organs. This idea led to preventative full-mouth extractions in patients assessed susceptible to any diseases. This practice was based on anecdotal evidence. Full mouth tooth extraction often failed to prevent systemic diseases confirming that the hypothesis was not valid. As a result, the Focal Infection Theory collapsed by the 1950s. Recently, periodontal research has focused on systemic conditions such as diabetes mellitus, cardiovascular disease, and CKD that have been shown to have an inflammation-linked pathogenesis. The underlying hypothesis is that periodontitis may contribute to overall systemic inflammation and affect the existing systemic disease status. Evidence has shown elevated serum levels of CRP as well as inflammatory cytokines such as IL-6 in patients with periodontal disease. The idea that periodontal infections can contribute to systemic inflammation is further validated by evidence indicating that treatment of periodontal disease can
reduce systemic levels of CRP, IL-6[68-70], and improve endothelial function[63, 70-72].

Based on the above, the underlying hypothesis of this research project was developed as shown below: CKD subjects compared to healthy controls have higher prevalence of periodontal infections that alter systemic inflammatory status leading to poor renal outcome.
II. Periodontitis in CKD Patients

A. Objectives

1. Hypothesis:
   CKD subjects have higher prevalence of severe periodontitis than healthy controls.

2. Specific Objectives:
   Using a population of stable CKD patients and healthy controls, we aimed to:

   a) Assess the prevalence of severe periodontitis in HD and pre-dialysis patients and compare to healthy controls.

   b) Assess the relationship between periodontal status and renal function.
B. **Introduction:**

Evidence on the prevalence of periodontitis in the CKD population is conflicting. In a cross-sectional study of 45 dialysis patients, Naugle and co-workers[73] found that 100% of subjects displayed some form of periodontal disease, although the majority of patients (64%) had mild periodontitis or gingivitis. Conversely, Marakoglu et al.[74] found no difference in clinical parameters of periodontal disease between 36 chronic renal failure patients on hemodialysis and 36 age and gender matched systemically healthy controls. The authors concluded that chronic renal failure did not seem to be a risk factor for more severe periodontal destruction. More recent studies have reported more severe periodontal destruction in renal failure patients compared to the general population[75]. In addition, CKD subjects are characterized by some well-established risk factors of periodontitis such as poor oral hygiene[76] and diabetes[77]. Because of the conflicting available evidence, it was the goal of this study to further explore the prevalence of periodontitis and its role on systemic inflammation in CKD patients.

C. **Materials & Methods:**
1. **Subject recruitment**

Based on studies by Borawski et al.[75] and Chen et al.[76], our power analysis estimated that 27 HD, 27 pre-dialysis CKD and 58 systemically healthy control patients would need to be recruited in order to identify a difference in periodontitis prevalence between HD, CKD and systemically healthy. However, since this was a one-year pilot feasibility study, we limited our sample size.

Twenty-one CKD patients, including twelve hemodialysis (HD) and nine stage 3-4 (pre-dialysis) CKD patients were recruited from the University of Connecticut Health Center (UCHC) Dialysis Unit and Nephrology Clinic after consultation with their nephrologist. In addition, thirteen non-CKD patients were recruited from UCHC personnel and served as healthy controls. Smokers were excluded from the study. The inclusion criteria were as follows: 1) a minimum of 15 teeth 2) no use of antibiotics within the past month 3) no periodontal treatment within the past year 4) absence of systemic infection 5) for the HD patients, no history of vascular access infection within the past month. The study was approved by the UCHC Institutional Review Board (IRB). All patients signed a consent form to enter the study.

2. **Data Collection**

**Medical Data**

Medical information of the CKD patients was extracted from hospital records using a standardized extraction form (see Appendix) that included age, gender,
ethnicity, weight, height, diabetes status, history of cardiovascular disease and hypertension, primary diagnosis, medication history including use of anti-hyperlipidemic or non-steroidal anti-inflammatory agents. Additionally, the most recent biochemical data were extracted from the charts including serum albumin, blood urea nitrogen (BUN), creatinine, ferritin level, total iron binding capacity (TIBC), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides. For HD patients, dialysis vintage was recorded. A detailed medical history questionnaire (see Appendix) was used in the control group.

Parameters of Periodontal Status

All patients received a full-mouth periodontal examination, which included clinical attachment loss (CAL), probing depth (PD), bleeding on probing (BOP), and plaque score (PS)\[78\] at six sites on all teeth. Based in part on work from Armitage[79] and Offenbacher[80], severe chronic periodontitis was defined as a minimum of 2 sites with pocket probing depth (PPD) ≥5mm, associated with ≥5mm CAL with ≥30% of sites exhibiting BOP. A subject was considered periodontally healthy if all of the following criteria were met: 1) full-mouth BOP <30% of sites, 2) fewer than 2 sites with PPD >4mm and 3) fewer than 2 teeth per quadrant with evidence of CAL ≥5mm.
3. Statistical analysis

All continuous variables were tested for normality. When a continuous variable was not normally distributed, it was treated with logarithmic transformation to achieve normality. Data were analyzed using Student's t test, ANOVA, and post-hoc Bonferroni testing. A p value of ≤0.05 was considered statistically significant. A computer software program\textsuperscript{1} was used for the statistical analyses.

D. Results:

1. Population characteristics

Population demographics of the test and control groups are presented in Table 2. The control group had more female and younger participants compared to the test group, although these differences did not reach statistical significance. The test group contained significantly more diabetics than the control group (35.0 percent versus 7.6 percent, p=0.0001).

2. General periodontal findings

Periodontal findings between CKD and control subjects are listed in Table 3 and Figures 1-3. Severe periodontitis was found in 47.4 percent of CKD subjects, compared to 15.4 percent of controls (p=0.02). Control subjects had significantly

\textsuperscript{1} SPSS 16, SPSS Inc.
fewer missing teeth than CKD subjects (mean 4.62±0.56 versus 8.09±3.23, p=0.01). Compared to healthy controls, CKD subjects had significantly higher mean PD (2.66±0.09mm versus 2.4±0.10mm, p=0.03) and CAL (3.21±0.18mm versus 2.47±0.10mm, p=0.004) (Figure 2). As shown in Figure 3, CKD subjects had significantly more sites with CAL≥5mm (mean 16.80±4.22 percent versus 2.55±1.5 percent, p=0.001). There were no significant differences in mean PS and BOP between CKD and control groups, although both parameters tended to be higher in the CKD group.

3. Periodontal findings and dialysis status

The periodontal data of the study population stratified into three groups based on CKD stage (CKD 3-4/Pre-dialysis, CKD 5/HD, Healthy) are shown in Table 4 and Figures 4-6. Although severe periodontitis was more prevalent in the hemodialysis and pre-dialysis groups compared to controls, the difference did not reach statistical significance. There were significant differences in PD (p=0.049), CAL (p=0.002), CAL≥5mm (p=0.016), and missing teeth (p=0.030) among the groups. Pre-dialysis patients had significantly more missing teeth than healthy controls. HD subjects had significantly higher mean PD (2.80±0.11mm versus 2.4±0.10mm, p<0.05), CAL (3.32±0.19mm versus 2.47±0.10mm, p<0.05), and CAL≥5mm (22.01±6.49 percent versus 2.55±1.5 percent, p<0.05) compared to control subjects. Pre-dialysis subjects also had higher PD and CAL compared to controls, but this difference only reached significance for CAL (3.06±0.244mm
versus 2.47±0.10mm, p<0.05). There was no statistical difference in mean BOP or PS among the three groups (p>0.05).

E. **Discussion**

In our study, severe periodontitis was prevalent in 47.4 percent of CKD patients, compared to 15.4 percent of controls. This difference was statistically significant. Additionally, when comparing continuous periodontal parameters, mean PD and CAL emerged as statistically significant. The difference in the mean values of continuous periodontal parameters (CAL, PD) between CKD and healthy groups was explained by the significantly higher percentage of diabetics in the CKD group as compared to the control group that has been shown to positively affect severity of periodontitis[81]. A possible solution to controlling this variable could be to exclude diabetics in our study population, although this would limit the number of CKD subjects as diabetes is the leading cause of renal failure, accounting for 44 percent of new cases in 2005[82]. Chuang and co-workers[83] 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.
While the CKD group had a higher prevalence of periodontitis, BOP was similar among the groups. This is likely due to the similar plaque scores between CKD and control patients, as presence of plaque has been associated with gingival inflammation, and mechanical removal of plaque is followed by clinical changes associated with healthy gingiva[84]. In spite of similar plaque scores, CKD patients had more periodontal destruction than healthy controls. This can be explained by the significantly higher percentage of diabetics in the CKD group, as diabetes is an established risk factor for gingivitis and periodontitis[48, 85]. It is unknown whether the dental plaque of CKD patients differs in composition from that of healthy controls, but studies comparing plaque pH of children with chronic renal failure compared to renal transplant or healthy children have shown the plaque from children with ESRD to be significantly more alkaline. It has been postulated that this difference in plaque pH may account for the low prevalence of caries in the CKD population[86], but it is unknown if this affects periodontal status. Also, CKD patients on HD are characterized by uremia, which has been associated with defects in lymphocyte and monocyte function[87]. Lymphocytes and monocytes play important roles in immune response, and defects in the function of these cells have been associated with aggressive forms of periodontal disease[88] and therefore may play a role in the increased amount of periodontal destruction seen in these patients.

The data on the prevalence of periodontitis in CKD populations are conflicting. Direct comparison of results to other studies is difficult owing to the different
definitions of periodontitis used by different research groups. The periodontitis
definition in this project was selected based on the current classification system
used by the American Academy of Periodontology[79] that defines severe
periodontitis as the presence of a single site with CAL ≥5mm. BOP was added to
this definition because a recent classification system [80] that identified new
clinical and distinct biologic phenotypes at the biofilm-gingival interface (BGI)
based upon DNA checkerboard analyses of plaque bacteria, serum
immunoglobulin G (IgG) titers to bacteria, and gingival crevicular fluid (GCF)
levels of inflammatory mediators includes BOP as one defining parameter. For
example, a BGI-deep lesion/moderate bleeding was defined as one or more sites
with PD ≥4mm and BOP extent scores between 10 and 50 percent.

The prevalence of severe periodontitis did not differ significantly among control,
hemodialysis, and pre-dialysis groups. Compared to HD patients, there were no
significant differences with pre-dialysis subjects in regard to any of the
periodontal parameters measured. Pre-dialysis patients had significantly higher
mean CAL compared to controls. These results are different than those from
Borawski[75], who found significantly higher mean CAL among hemodialysis
patients compared to pre-dialysis patients. A direct comparison of prevalence of
periodontitis to our results could not be performed owing to differences in the
definition of periodontal disease, but pre-dialysis patients in Borawski’s study had
significantly higher community periodontal index and treatment needs (CPITN)
scores than those patients on hemodialysis or controls, indicating an increased
prevalence and severity of periodontal disease in this population. The differences in sample size compared with our pilot study could also account for the conflicting results. Further large-scale studies with a standardized approach to evaluating the periodontal status of pre-dialysis populations are needed.

The cross-sectional design of this study prevents us from determining any cause-effect relationships between periodontal disease and chronic kidney disease. It is possible that this association may be due to a direct cellular effect on the nephron unit or its vasculature by periodontal pathogens. While a direct cellular invasion of periodontal pathogens in renal tissue has yet to be shown, periodontal pathogens have been shown to invade coronary and aortic endothelial cells[89, 90]. Furthermore, periodontitis patients have been shown to have chronic and recurrent episodes of low-level bacteremia[91, 92]. Some have hypothesized that bacteria may be filtered out of the blood at the glomerulus, where these organisms or their products may invade capillary endothelium or mesangial cells/matrix[93]. Future studies are needed to confirm the role of periodontal pathogens on renal tissue.
III. Serum Inflammatory Markers in CKD Patients
A. **Objectives:**

1. **Hypothesis:**

   Inflammatory periodontal disease in CKD patients contributes to systemic inflammatory response, which may affect clinical outcomes.

2. **Specific Objectives:**

   Using a population of stable CKD patients and healthy controls, we aimed to:

   a) Assess the levels of the systemic inflammatory markers, IL-6 and CRP, in the presence or absence of periodontal infection in HD and pre-dialysis CKD populations compared to healthy controls.
B. **Introduction:**

The role of inflammation in the pathogenesis of periodontal disease and other systemic diseases has been documented[94-96]. Although the exact pathogenic mechanism remains unclear, one hypothesis is that elevated amounts of inflammatory cytokines are released locally from the diseased periodontium into the bloodstream, leading to an increase in serum cytokines at the systemic level, thus contributing to disease outcomes. Diseased periodontal tissues have been shown to possess higher levels of IL-6 than healthy tissues[97, 98], and serum CRP has been shown to be elevated in patients suffering from periodontitis[99]. Additionally, evidence has shown that treatment of periodontal disease may be associated with reduced serum levels of inflammatory markers and corresponding improvement in glycemic control[100] and endothelial function[63], although the evidence is conflicting.

The leading cause of mortality in CKD patients is cardiovascular disease, regardless of CKD stage [101, 102] [103]. Elevated levels of inflammatory markers such as CRP and IL-6 are known predictors of cardiovascular outcomes in the HD population[104], and are linked to hypoalbuminemia, malnutrition, erythropoietin resistance and increased mortality[105, 106].

It has been recognized that approximately 30-50% of CKD[107] [108] patients have evidence of a systemic inflammatory response which may be caused by
persistent infections[27]. Since periodontitis as a chronic persisting infection has been associated with systemic elevation of inflammatory markers [99], it may also predict poor outcomes in CKD populations. Therefore, we hypothesize that severe periodontitis may represent a "non-traditional" risk factor for elevated systemic inflammation in CKD populations.

C. **Materials & Methods:**

1. **Subject recruitment**

Based on studies by Borawski et al.[75] and Rao et al.[104], our power analysis estimated it would be necessary to recruit 43 HD, 43 pre-dialysis, and 15 healthy controls for CRP assessment and 29 HD, pre-dialysis, and healthy controls for IL-6 assessment. For the purposes of this analysis in this pilot feasibility study, the same group of subjects described in Objective 1 was used. The subjects signed a consent form that was approved by the Institutional Review Board (IRB) as described before. Medical and biochemical data were retrieved from the medical records as described in Objective 1.

2. **Blood sampling and analysis**

In HD subjects, blood samples were drawn from the arterial end of the vascular access immediately before initiation of the HD and then stored at -70° until
In pre-dialysis and control subjects, 15 ml venous blood was collected prior to the oral clinical examination by a certified phlebotomist.

Within 2 hours of blood collection, sera were separated after clotting for 30 minutes at 4°C, followed by centrifugation at 3,000 x g for 15 minutes. Aliquots were stored at -80°C until testing. Sera were coded and analyzed in duplicate by ELISA\(^1\) without the knowledge of the periodontal disease or CKD status of the study participants. The IL-6 and CRP assay analytical sensitivities were 2.0 pg/ml and <0.3 mg/L, respectively, and the variation in protein values within runs was <1% for both assays.

### 3. Statistical analysis

Continuous variables were tested for normality and logarithmically transformed if skewed. IL-6 and CRP levels were compared among the groups by Student’s t test, ANOVA, and post-hoc Bonferroni test. Pearson’s correlation coefficients were calculated to test the associations between serum CRP, serum IL-6, and periodontal variables. Any variables that had an association with \(r \geq 0.5\) were included at the multivariate regression analysis as confounders. A multivariate linear regression model was run, using serum CRP and IL-6 as dependent variables and testing periodontitis as a predictor variable and adjusting for confounders based on the significance of the correlation coefficient. A \(p\) value of \(\leq 0.05\) was considered statistically significant.

\(^1\) Diagnostic Products, Los Angeles, CA.
D. Results:
1. Serum inflammatory markers and CKD status

Serum CRP and IL-6 levels for control and CKD patients are listed in Table 5 and shown in Figures 7 and 8. CKD patients had a higher mean CRP levels (median 3.87, range 0.30-78.35μg/ml) compared to controls (median 1.41, range 0.42-18.00μg/ml). This difference was statistically significant (p=0.014). Similarly, IL-6 levels were higher in CKD patients (median 8.72, range 0.60-9.92pg/ml) when compared to control subjects (median 4.00, range 2.00-5.82pg/ml). This difference was also statistically significant (p=0.038).

Table 6 and Figures 9 and 10 show CRP and IL-6 levels in subjects according to renal status (hemodialysis, pre-dialysis, and controls). There were significant differences between the groups for both CRP and IL-6. In regard to serum CRP levels, control subjects (median 1.41, range 0.42-18.00μg/ml) had lower values than hemodialysis (median 5.78, range 1.87-41.80μg/ml) and pre-dialysis (median 2.48, range 0.30-78.35μg/ml) patients. This difference reached statistical significance for HD patients only (p<0.05). There were no significant differences between hemodialysis and pre-dialysis groups (p>0.05). Serum IL-6 levels were significantly elevated in hemodialysis patients (median 10.98, range 6.01-29.35pg/ml) compared to pre-dialysis patients (median 4.00, range 0.60-9.92pg/ml, p<0.05) and control subjects (median 4.00, range 2.00-5.92pg/ml, p<0.05). There were no significant differences between pre-dialysis and control subjects (p>0.05).
2. Serum inflammatory markers and periodontal status

Table 7 and Figures 11-12 show CRP and IL-6 levels in subjects stratified based on the periodontal status. Subjects with severe periodontitis had lower serum CRP levels (median 2.935, range 0.21-41.8μg/ml) than periodontally-healthy subjects (median 3.26, range 0.42-78.32μg/ml), but this difference was not significant (p>0.05). In contrast, IL-6 levels in subjects with severe periodontitis (median 6.175, range 2.00-29.35pg/ml) were significantly higher compared to subjects without periodontitis (median 4.63, range 2.00-11.35, p=<0.05).

3. Association between inflammatory markers and periodontal parameters

Correlations between serum IL-6/CRP levels and periodontal parameters are presented in Table 8. Both serum IL-6 and CRP levels were significantly related to PS (r=0.385; p=0.039 and r=0.372; p=0.047, respectively). There was a trend toward significance for the associations between serum IL-6 levels and CAL (r=0.281, p=0.140). In contrast to IL-6, serum CRP levels were highly related to CAL (r=0.500, p=0.006) as well as CAL≥5mm (r=0.409, p=0.027). There was also a trend toward significance for the relationships between serum CRP levels and BOP (r=0.294, p=0.122) and PD (r=0.307, p=0.106). Furthermore, there was a significant correlation between periodontal status and serum IL-6 (r=0.441, p=0.045) as well as CRP and IL-6 (r=0.450, p=0.041) among CKD patients.
Multivariable linear regression analysis models were constructed to assess the interaction between medical and periodontal parameters and serum IL-6 and CRP levels in the CKD patients. Using serum IL-6 as a dependent variable (Table 9), HD status was a significant predictor for elevated serum IL-6 levels (p=0.029), but periodontal status was not (p=0.350). The interaction between HD and periodontal status was also not significant (p=0.161). When serum CRP was used as the dependent variable (Table 10), there was a significant effect of gender (p=0.028) and BMI (p=0.013), and dialysis status was a significant predictor of elevated serum CRP (p=0.012), but periodontal status was not (p=0.432). The interaction between HD and periodontal status did not have a significant effect on serum CRP levels (p=0.256).

E. Discussion

In our study, both serum CRP levels and IL-6 levels were higher in CKD subjects compared to controls. CKD is characterized by a chronic state of inflammation[33], so these results were expected and are consistent with those reported by others[22-24]. The sources of inflammation in CKD patients are still under investigation, but clotted access grafts[29], atherosclerotic processes[109], and persistent infections[27, 28] have all been suggested to be contributory factors. Residual renal function may also have an important role in the inflammatory process. For example, serum IL-6, IL-8, and TNF-alpha levels have been shown to be elevated in HD patients compared to healthy
controls[25]. In addition, patients on peritoneal dialysis have been reported to have increased CRP levels during the first year of dialysis[110]. Animal studies also suggest a reduced clearance of pro-inflammatory cytokines when renal function is impaired[111, 112].

Serum CRP levels were significantly higher in HD patients compared to controls. While pre-dialysis patients had higher CRP levels compared to controls, this difference did not reach statistical significance. Other studies have found CRP levels to be elevated in pre-dialysis patients[113], and several researchers[113-115] have found an inverse relationship between GFR and CRP levels in pre-dialysis patients. The exact reason why there was no significant difference in CRP levels between HD and pre-dialysis patients cannot be explained. However, the incidence of elevated serum CRP levels has been shown to be different among different geographical populations[116], indicating that causes other than dialysis-related factors such as nutrition and lifestyle can also play a role in serum CRP levels. Our limited sample size could also explain these trends as well as our inability to discern a statistically significant difference between the two CKD populations.

Serum IL-6 levels were significantly higher in HD patients compared to both pre-dialysis patients and healthy controls. Our findings of increased IL-6 levels in HD patients is in agreement with others who have found plasma IL-6 to be elevated in these patients[117, 118]. The lack of a statistically significant difference in IL-6
levels between pre-dialysis patients and controls in some of our analysis is in contrast to what has been reported by others[119].

IL-6 levels have been shown to predict mortality in both HD and pre-dialysis patients[42, 104, 118] and may be a better predictor of mortality than CRP[119]. This leads one to question whether a medical or pharmacological intervention can alter this cytokine imbalance to improve outcomes. Statins and ACE-inhibitor drugs administered to CKD patients can lower IL-6 levels in both non-renal and CKD patients[120-123], but it is unknown if this affects mortality outcomes.

As expected, serum IL-6 levels were higher in patients with severe periodontitis compared to subjects without periodontitis. This is consistent with the findings reported by others[97, 98]. While there were statistically significant differences in IL-6 levels between periodontitis and non-periodontitis groups, this was not the case for CRP levels. The finding that CRP levels were higher in non-periodontitis patients compared to periodontitis patients is unexpected. Other authors[99] have shown CRP to be elevated in patients suffering from periodontitis, and treatment of periodontitis has been shown to decrease CRP levels in systemically healthy patients[68], so our findings are inconsistent with previous reports. This could be accounted for by our limited sample size (n=33) coupled with the limited number of patients displaying severe periodontitis (n=12). The mechanism for the differences in serum inflammatory mediators in the presence
of diseased and healthy periodontal tissue is still under investigation. One possibility is that these mediators are produced from the periodontium itself. It has been shown that gingival fibroblasts from chronic periodontitis lesions produce greater amounts of IL-6 than healthy controls[97]. IL-6 has also been found to be elevated in the gingival crevicular fluid[124] and serum[68] of chronic periodontitis patients. This may be due to polymorphisms resulting in an increased expression of the IL-6 (-174) gene in the presence of periodontal infections[125]. It has been hypothesized that this increase in pro-inflammatory mediators could theoretically spill over into the circulation, thus inducing systemic effects[126].

Both serum IL-6 and CRP levels were significantly correlated with plaque scores. It has been postulated that high-responder individuals produce high levels of inflammatory mediators and cytokines as part of their host inflammatory response to the presence of plaque[127, 128] and, consequently, these individuals are more susceptible to periodontitis. Based on this evidence, however, we would not expect a direct relationship between inflammatory mediator level and plaque score. Other authors[74] have found no difference in gingival index scores between chronic renal failure patients on HD and systemically healthy control patients with similar levels of plaque, suggesting that HD patients may exhibit a similar inflammatory response to dental plaque as healthy patients.
The significance of HD status as an independent predictor of serum IL-6 and CRP levels in the multivariate analysis was expected, as hemodialysis patients have been shown to have elevated serum inflammatory markers compared to non-hemodialysis patients[21-24]. In our study, periodontal status was not a predictor of serum IL-6 or CRP. However, multiple studies performed on non-CKD populations have shown that serum IL-6 and CRP levels are elevated in periodontal patients when compared to periodontally-healthy controls[65-67], and that periodontal treatment can reduce levels of these markers[65]. Further studies on CKD populations are needed to verify our findings. The interaction between the CKD and periodontal status was not significant for either inflammatory marker. The limited sample size of our CKD (n=21) and periodontitis (n=12) subjects in this pilot study could account for these findings.

A limitation of our study was the sample size and the cross-sectional design of our study does not allow us to make any conclusions regarding a cause and effect relationship between periodontal disease and systemic inflammation. Further large-scale, intervention studies are needed.
IV. Concluding Remarks
1. Severe periodontitis was found to be significantly more prevalent in a stable CKD population compared to healthy controls. There was no statistically significant difference in prevalence of severe periodontitis between hemodialysis, pre-dialysis, and control subjects.

2. Serum IL-6 and CRP levels were statistically significantly higher in CKD patients compared to healthy controls. For serum IL-6, hemodialysis patients had significantly higher levels compared to pre-dialysis and control patients. Serum CRP levels were significantly higher in hemodialysis and pre-dialysis patients compared to controls. There were no significant differences in CRP or IL-6 levels between pre-dialysis and control subjects.

3. Subjects with severe periodontitis had higher serum levels of IL-6 compared to periodontally-healthy subjects. There were no significant differences with regards to serum CRP levels.

4. HD status was a significant independent predictor of both serum IL-6 and CRP levels in CKD patients.
V. Index (Tables and Figures)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular Filtration Rate (GFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At increased risk</td>
<td>Risk factors for kidney disease (e.g., diabetes, high blood pressure, family history, older age, ethnic group)</td>
<td>More than 90</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage (protein in the urine) and normal GFR</td>
<td>More than 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage and mild decrease in GFR</td>
<td>60 to 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30 to 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15 to 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (dialysis or kidney transplant needed)</td>
<td>Less than 15</td>
</tr>
</tbody>
</table>
Table 2: Population characteristics of CKD and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD Subjects (n=21)</th>
<th>Control Subjects (n=13)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±9.7</td>
<td>54±12</td>
<td>0.46</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>42.5</td>
<td>46.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetics (%)</td>
<td>35.0</td>
<td>7.6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 3: Periodontal characteristics of CKD and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD Subjects (n=21)</th>
<th>Control Subjects (n=13)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe periodontitis (%)</td>
<td>47.6</td>
<td>15.4</td>
<td>0.02</td>
</tr>
<tr>
<td>PD (mm)</td>
<td>2.66±0.09</td>
<td>2.4±0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>CAL (mm)</td>
<td>3.21±0.18</td>
<td>2.47±0.10</td>
<td>0.004</td>
</tr>
<tr>
<td>BOP (%)</td>
<td>16.06±3.4</td>
<td>15.47±3.82</td>
<td>0.45</td>
</tr>
<tr>
<td>PS (%)</td>
<td>53.35±8.05</td>
<td>43.79±7.07</td>
<td>0.19</td>
</tr>
<tr>
<td>Missing teeth (n)</td>
<td>8.09±3.23</td>
<td>4.62±0.56</td>
<td>0.01</td>
</tr>
<tr>
<td>Sites CAL≥5mm (%)</td>
<td>16.80±4.22</td>
<td>2.55±1.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Figure 1: Percent of subjects with severe periodontitis

Advanced Periodontitis

* p ≤ 0.05

Figure 2: Comparison of periodontal parameters (PPD, CAL) between CKD and control groups

Periodontal Parameters

* p ≤ 0.05
Figure 3: Comparison of periodontal parameters (BOP, PS, CAL≥5) between CKD and control groups.

* p ≤ 0.05
Table 4: Periodontal characteristics of subjects according to renal status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemodialysis Subjects (n=12)</th>
<th>Pre-dialysis Subjects (n=9)</th>
<th>Control Subjects (n=13)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe periodontitis (%)</td>
<td>45.4</td>
<td>44.4</td>
<td>15.4</td>
<td>0.13</td>
</tr>
<tr>
<td>PD (mm)</td>
<td>2.80±0.11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.57±0.12</td>
<td>2.4±0.10</td>
<td>0.049</td>
</tr>
<tr>
<td>CAL (mm)</td>
<td>3.32±0.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.06±0.24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.47±0.10</td>
<td>0.002</td>
</tr>
<tr>
<td>BOP (%)</td>
<td>21.74±4.86</td>
<td>9.91±3.59</td>
<td>15.47±3.82</td>
<td>0.174</td>
</tr>
<tr>
<td>PS (%)</td>
<td>59.42±9.88</td>
<td>40.07±12.30</td>
<td>43.79±7.07</td>
<td>0.300</td>
</tr>
<tr>
<td>Missing teeth (n)</td>
<td>6.42±1.03</td>
<td>10.62±2.65&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.62±0.56</td>
<td>0.030</td>
</tr>
<tr>
<td>Sites CAL≥5mm (%)</td>
<td>22.01±6.49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.57±5.81</td>
<td>2.55±1.5</td>
<td>0.016</td>
</tr>
</tbody>
</table>

<sup>a</sup> - p≤0.05 between HD and control subjects
<sup>b</sup> - p≤0.05 between pre-dialysis and control subjects
<sup>c</sup> - p≤0.05 between HD and pre-dialysis subjects
Figure 4: Percent of subjects with severe periodontitis according to renal status

Advanced Periodontitis

Figure 5: Comparison of periodontal parameters (PPD, CAL) according to renal status

Periodontal Parameters

* p ≤ 0.05 compared to control group
Figure 6: Comparison of periodontal parameters (BOP, PS, CAL≥5) according to renal status

* p ≤ 0.05 compared to control group

Table 5: Serum inflammatory markers in CKD and control subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD Subjects (n=21)</th>
<th>Control Subjects (n=13)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>CRP (μg/ml)</td>
<td>3.87</td>
<td>0.30-78.35</td>
<td>1.41</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>8.72</td>
<td>0.60-9.92</td>
<td>4.00</td>
</tr>
</tbody>
</table>
Figure 7: Comparison of serum CRP levels between CKD and control subjects

* $p \leq 0.05$
Figure 8: Comparison of serum IL-6 levels between CKD and control subjects

* p < 0.05

Table 6: Serum inflammatory markers in subjects according to renal status

<table>
<thead>
<tr>
<th>Variable</th>
<th>HD Subjects (n=12)</th>
<th>Pre-dialysis Subjects (n=9)</th>
<th>Control Subjects (n=13)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>CRP (µg/ml)</td>
<td>5.78±</td>
<td>1.87-41.80</td>
<td>2.48</td>
<td>0.30-78.35</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>10.98±</td>
<td>6.01-29.35</td>
<td>4.00</td>
<td>0.60-9.92</td>
</tr>
</tbody>
</table>
a - $p \leq 0.05$ between HD and control subjects

b - $p \leq 0.05$ between pre-dialysis and control subjects

c - $p \leq 0.05$ between HD and pre-dialysis subjects
Figure 9: Comparison of serum CRP levels according to renal status

Serum CRP Levels

* $p \leq 0.05$ compared to control group

Figure 10: Comparison of serum IL-6 levels according to renal status

Serum IL-6 Levels

* $p \leq 0.05$ compared to control group

** $p \leq 0.05$ compared to pre-dialysis group
Table 7: Serum inflammatory markers in subjects according to periodontal status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Periodontitis Subjects (n=22)</th>
<th>Periodontitis Subjects (n=12)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>CRP (µg/ml)</td>
<td>3.26</td>
<td>0.42-78.32</td>
<td>2.935</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>4.63</td>
<td>2.00-11.35</td>
<td>6.175</td>
</tr>
</tbody>
</table>

Figure 11: Comparison of serum CRP levels according to periodontal status
Figure 12: Comparison of serum IL-6 levels according to periodontal status

Serum IL-6 Levels

* p ≤ 0.05
Table 8: Correlations between inflammatory markers and patient characteristics and periodontal variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum IL-6</th>
<th>Serum CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>R</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.603</td>
</tr>
<tr>
<td>Gender</td>
<td>R</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.710</td>
</tr>
<tr>
<td>BOP</td>
<td>R</td>
<td>0.166</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.388</td>
</tr>
<tr>
<td>PS</td>
<td>R</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.039</td>
</tr>
<tr>
<td>PD</td>
<td>R</td>
<td>0.205</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.287</td>
</tr>
<tr>
<td>CAL</td>
<td>R</td>
<td>0.281</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.140</td>
</tr>
<tr>
<td>CAL≥5mm</td>
<td>R</td>
<td>0.189</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.326</td>
</tr>
</tbody>
</table>
Table 9: Multivariable linear regression analysis in CKD patients with serum IL-6 as the dependent variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.144</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.938</td>
</tr>
<tr>
<td>Gender</td>
<td>0.436</td>
</tr>
<tr>
<td>BMI</td>
<td>0.780</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>0.662</td>
</tr>
<tr>
<td>Dialysis status (yes/no)</td>
<td>0.029</td>
</tr>
<tr>
<td>Periodontitis status (yes/no)</td>
<td>0.350</td>
</tr>
<tr>
<td>Dialysis status*Periodontal status</td>
<td>0.161</td>
</tr>
</tbody>
</table>
Table 10: Multivariable linear regression analysis in CKD patients with serum CRP as the dependent variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.397</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.165</td>
</tr>
<tr>
<td>Gender</td>
<td>0.028</td>
</tr>
<tr>
<td>BMI</td>
<td>0.013</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>0.741</td>
</tr>
<tr>
<td>Dialysis status (yes/no)</td>
<td>0.012</td>
</tr>
<tr>
<td>Periodontitis status (yes/no)</td>
<td>0.432</td>
</tr>
<tr>
<td>Dialysis status * Periodontal status</td>
<td>0.256</td>
</tr>
</tbody>
</table>
VI. Appendix

1) Medical History Questionnaire for Control Subjects

University of Connecticut Health Center
School of Dental Medicine, University Dentists

MEDICAL HISTORY QUESTIONNAIRE
(Parent or Guardian to answer for child under 18 years of age)

Name __________________________ M F Date of Birth __________
Address __________________________
Telephone: (Home) __________ (Work) __________ Height __________ Weight __________
Today’s Date __________ Occupation __________

Answer all questions by circling either YES or NO. Fill in blank spaces when indicated. ANSWERS ARE FOR OUR RECORDS ONLY AND ARE CONFIDENTIAL.

1. My last medical physical examination was on (approx.) __________

2. The name & address of my personal physician is __________

3. Are you now under the care of a physician __________
   YES NO
   If yes, what is the condition being treated __________

4. Have you had any serious illness or operation __________
   YES NO
   If yes, what was the illness or operation __________

5. Have you been hospitalized within the past 5 years __________
   YES NO
   If yes, what was the problem __________

6. Do you have or have you had any of the following diseases or problems:

   __________ Rheumatic fever or rheumatic heart disease __________ YES NO
   __________ Heart abnormalities present since birth __________ YES NO
   __________ Cardiovascular disease (heart trouble, heart attack, angina, stroke, high
   blood pressure, heart murmur) __________ YES NO
      Do you have discomfort or pressure in the chest upon exertion __________ YES NO
      Are you ever short of breath after mild exercise __________ YES NO
      Do your ankles swell __________ YES NO
      Do you get short of breath when you lie down, or do you require extra pillows
      when you sleep __________ YES NO
      Have you been told you have a heart murmur __________ YES NO

   __________ Asthma or hay fever __________ YES NO
   __________ Hives or a skin rash __________ YES NO
   __________ Fainting spells or seizures __________ YES NO
   __________ Diabetes __________ YES NO
   __________ Jaundice or liver disease __________ YES NO
   __________ Hepatitis __________ YES NO
   __________ Arthritis or other joint problems __________ YES NO
   __________ Stomach ulcers __________ YES NO
   __________ Kidney trouble __________ YES NO
   __________ Dialysis patient __________ YES NO
   __________ Tuberculosis __________ YES NO
   __________ Do you have a persistent cough or cough up blood __________ YES NO
   __________ Venereal disease __________ YES NO
   __________ AIDS/HIV __________ YES NO
   __________ Other (list) __________ YES NO

7. Have you had surgery or radiation treatment for a tumor, cancer or other condition
   of your head or neck __________ YES NO

8. Have you had abnormal bleeding associated with previous extractions, surgery or trauma __________ YES NO
9. Do you have any blood disorder such as anemia, including sickle cell anemia ....... YES NO
10. Are you a hemophiliac ............................................................... YES NO
11. Are you a present or past IV drug user ............................................... YES NO
12. Are you at increased risk for the HIV virus or AIDS .................................. YES NO
13. Are you taking any drug or medicine ................................................... YES NO

14. Are you taking any of the following:
   - Antibiotics or sulfa drugs...................................................... YES NO
   - Anticoagulants (blood thinners)............................................. YES NO
   - Medicine for high blood pressure............................................. YES NO
   - Steroids (Prednisone, Cortisone)............................................. YES NO
   - Drugs that change your mood................................................ YES NO
   - Aspirin .................................................................................... YES NO
   - Insulin, tolbutamide (Orinase) or similar drugs.......................... YES NO

15. Do you suffer from any birth defect or other disability.................................. YES NO

16. Are you allergic or have you reacted adversely to:
   - Local anesthetics .................................................................... YES NO
   - Penicillin or other antibiotics................................................... YES NO
   - Sulfa drugs .............................................................................. YES NO
   - Aspirin .................................................................................... YES NO

17. Have you had any serious trouble associated with any previous dental treatment ....... YES NO
    If yes, explain ..............................................................................

18. Do you have any disease, condition, or problem not listed above.......................... YES NO
    If so, please explain .....................................................................

19. Does your employment expose you regularly to x-rays or other ionizing radiation ......... YES NO

20. Are you wearing contact lenses .................................................................... YES NO

21. Are you pregnant or have you recently missed a menstrual period ...................... YES NO

22. Are you presently breast feeding .................................................................... YES NO

Chief dental complaint (why did you come to the dentist today?)

TO THE BEST OF MY KNOWLEDGE, THE ABOVE INFORMATION IS COMPLETE AND ACCURATE

__________________________
Signature of Patient or Legal Guardian

__________________________
Signature of Dentist

HEALTH HISTORY UPDATED:
Date:

2) Medical Data Extraction Form for CKD Subjects
Hemodialysis and Pre-dialysis Patient
Chart Review

SECTION 1: PARTICIPANT DEMOGRAPHICS

1. Pt ID: ___________________ (3 digit #)
2. DOB: ____/____/____
3. Ethnicity:
   5. Am Ind/Alaska Native [ ] 6. Hispanic [ ] 7. Unknown [ ]
4. Gender: male [ ] female [ ]

SECTION 2: MEDICAL HISTORY

5. Does the patient have history of diabetes? Y [ ] N [ ]
   If yes, Type I [ ] Type II [ ] Insulin-requiring [ ]
6. Is the patient a smoker? Current [ ] Former [ ] Never smoked [ ]
7. Weight _______ Height: _______ BMI: _______
8. Menopause Y [ ] N [ ]
9. Hyperlipidemia Y [ ] N [ ]
10. Infection within the last 2 months (vascular access/fistula, UTI, bronchitis, peritonitis, pneumonia, abdominal abscess etc).

11. Does patient have a history of cardiovascular disease? Y [ ] N [ ]
    If yes check appropriate diagnosis
    Heart failure [ ] Coronary heart disease [ ] Aortic [ ]
    Coronary artery bypass grafting (CABG) [ ]
    Angina [ ] CAD [ ] Cardiovascular disease, stroke or sarnaic attack [ ]

Date: __________/_______/_______
Reviewer: ________________
12. Does the patient have history of hypertension?  
   Y [ ]  N [ ]

13. What is the patient's pre-dialysis kidney disease diagnosis? (Please specify etiology of underlying disease)

SECTION 3: Biochemical data (Most recent)

14. Serum albumin
15. Blood urea nitrogen (BUN):
16. Creatinine:
17. Ferritin level:
18. Total Iron Binding Capacity (TIBC):
19. Total cholesterol:
20. HDL-cholesterol:
21. LDL-cholesterol:
22. Triglycerides:
23. Dialysis adequacy (Kt/V):
   (only for hemodialysis subjects)
24. Dialysis vintage (years on dialysis):
   (only for hemodialysis subjects)

SECTION 4: Medication

25. Has the patient been on non-steroidal anti-inflammatory medication within the last month?  
   Y [ ]  N [ ]
   Dose ______  Duration: ______

26. Has the patient ever been on anti-hyperlipidemic meda?  
   Y [ ]  N [ ]
   Dose ______  Duration: ______

27. Please attach medication list.
28. Please attach SF-36 questionnaire
3) Abbreviations used

ANOVA – Analysis of variance

AV – Arteriovenous

BGI – Biofilm-gingival interface

BMI – Body mass index

BOP – Bleeding on probing

BUN – Blood urea nitrogen

CAL – Clinical attachment loss

CKD – Chronic kidney disease

CRP – C reactive protein

CVD – Cardiovascular disease

ELISA – Enzyme-linked immunosorbent assay

ESRD – End stage renal disease

GFR – Glomerular filtration rate

HD – Hemodialysis

HDL – High density lipoprotein

Ig - Immunoglobulin

IL – Interleukin

IRB – Institutional Review Board
LDL – Low density lipoprotein

PPD – Pocket probing depth

TIBC – Total iron binding capacity

UCHC – University of Connecticut Health Center
VII. Bibliography


