Title

In a population of patients with compromised renal function, is there a correlation in periodontal status using systemic markers of eGFR, HbA1C, and serum albumin to creatinine ratio

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In a population of patients with compromised renal function, is there a correlation in periodontal status using systemic markers of eGFR, HbA1C, and serum albumin to creatinine ratio

By

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THESIS

Submitted in partial satisfaction of the requirements for the degree of

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DEDICATION

I would like to dedicate this Masters Thesis to my family for inspiring me to enter into this great profession. I would also like to dedicate this thesis to my girlfriend, who has supported me through all the great and difficult times throughout my dental career.

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I would like to thank Drs. Ryder, Miller, and Kiurtsidis for heading my Masters Thesis Committee. I appreciate all the guidance, advice, and help you all have generously donated to me along the way during this challenging process. I would also like to thank all my clinical faculty for the time and dedication put into teaching myself and helping to move forward the profession.

ABSTRACT

In a population of patients with compromised renal function, is there a correlation in periodontal status using systemic markers of eGFR, HbA1C, and serum albumin to creatinine ratio

Erik Low, DMD

***Purpose*:**

The aim of this study is to investigate, in a population of patients with compromised renal function, is there a correlation in periodontal status using systemic markers of estimated glomerular filtration rate (eGFR), HbA1C, and serum albumin to creatinine ratio.

***Methods*:**

Patients' were screened for kidney disease and had to have an eGFR <60 ml/min/m^2. They were also screened for periodontal disease and had to have been diagnosed with moderate/severe periodontal disease according to CDC/AAP guidelines and have 30% BOP. After patients' met inclusion/exclusion criteria, a thorough periodontal exam was performed at baseline which included: probing depths (PD), gingival margin position (GM), clinical attachment level (CAL), plaque index (PI), gingival index (GI), and bleeding on probing (BOP) at six sites (MB, B, DB, DL, L, and ML) per tooth for every tooth. Additionally, blood and urine samples were taken at baseline as well to measure eGFR, HbA1c, and serum albumin to creatinine ratio. Simple statistics such as means, medians, and standard deviations were calculated for the entire population for both periodontal and kidney parameters. Also spearman rank correlations were calculated to determine if there were any associations between periodontal disease and chronic kidney

disease. Lastly, surrogate markers of periodontal disease such as PD and CAL were stratified into categories to determine if there was any correlation with chronic kidney disease.

Results:

After applying the inclusion and exclusion criteria, 21 subjects entered the study. For correlation between kidney markers and periodontal markers, the eGFR was moderately positively correlated with average CAL ($r = 0.46956$, $p \leq 0.0317$), and HBA1C (%) was moderately negatively associated with average PI ($r = 0.51205$, $p \leq 0.0176$). When stratifying the data into PD and CAL categories, there were some differences that could be seen amongst the surrogate markers for chronic kidney disease, but none were statistically significant. Additionally, there was no statistically significant correlation between BOP % and markers of kidney function assessed in this study such as eGFR, HbA1c, and serum albumin to creatinine ratio %.

Conclusions:

There was no evidence in this study that supported the hypothesis that the severity of periodontal disease is correlated to the severity of chronic kidney disease and vice versa. The results of this study need to be interpreted with caution due to the small population ($n = 21$). Therefore, larger scale studies with more subjects, which look at populations more representative of the population as a whole, need to be conducted to determine if there is a correlation between periodontal disease and chronic kidney disease (CKD). Also, longitudinal studies of this magnitude need to be carried out to see if improvements of markers of one disease affect markers of the other.

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INTRODUCTION

In the last quarter century, there has been growing publicity and mounting evidence that periodontal disease may contribute or be associated to a number of acute and chronic systemic illnesses according to Linden *et al.,* 2013. Specifically, periodontal disease has recently been implicated as a novel focus for impacting chronic kidney disease (CKD). A biologically plausible link between periodontal disease and these systemic illnesses are of course, infection and inflammation. The inflammation that periodontal disease causes in the oral cavity may also contribute to the chronic systemic inflammatory burden of the body (Van Dyke *et al.,* 2013). Periodontal pathogens have the ability to enter the systemic circulation through normal daily activities such as tooth brushing and even chewing (Geerts *et al.,* 2002 and Ebersole *et al.,* 2010). Consequently, the circulating bacterial coating can bind specific receptors found throughout the body and the kidney. Once the bacteria bind to receptors in the kidney, these receptors become activated and launch an inflammatory cascade that may lead to deterioration in renal function and also exacerbate periodontal disease.

Although, periodontal infection is mainly chronic in nature, the host responds to it with both innate and adaptive immunity. Part of the innate immunity is the systemic release of acute phase proteins such as C-reactive protein (CRP). A study by Loos *et al.,* 2005, showed that acute phase proteins and systemic inflammation is present in periodontitis patients. Additionally, Ebersole *et al.,* 1997 observed in rapidly progressing periodontitis patients a CRP level of 9.0mg/L vs 2mg/L in controls. In another study by Loos *et al.,* 2000, they discerned the highest CRP values were found in patients with a generalized form of periodontitis (median 1.45 mg/l); for patients with a

more localized form of periodontal disease, the median CRP value was 1.30 mg/l, while healthy controls presented with a median of 0.90 mg/l. This also demonstrated that CRP could behave in a dose-dependent manner, where on average, CRP levels increase with an increase in disease extent and severity. Therefore, the systemic inflammation that periodontal disease causes has been shown to have associations with a multitude of systemic illnesses such as atherosclerosis, heart disease, stroke, diabetes, respiratory disease, Alzheimer's disease, and chronic kidney disease. This paper will focus on the possible link between periodontal disease and chronic kidney disease.

Chronic kidney disease (CKD) is an overall encompassing term that includes a number of diverse renal diseases including dialysis and kidney transplant patients. Other causes can be from glomerulonephritis (nephritic/nephrotic syndrome), interstitial nephritis, unresolved acute tubular necrosis, toxicity from exposure to chemicals or drugs, obstructive uropathy, nephrolithiasis, and effects from systemic diseases such as systemic lupus erythematosis, scleroderma, and multiple myeloma (Scannapieco *et al.,* 2008). CKD is defined as either kidney damage, from either pathological abnormalities or markers of damage, or an estimated glomerular filtration rate (eGFR) <60 ml/min/m^2 for more than 3 months (National Kidney Foundation 2002). The gold standard in determining GFR in patients is to measure the clearance of inulin since it is not secreted by the renal tubules, but this remains an impractical clinical test. Therefore, clinicians typically use the serum creatinine as an indirect measurement and use a creatinine based formula to calculate GFR. There is generally a high degree of physiologic variability in GFR of normal patients, making it difficult to determine normal GFR. Therefore, the National Kidney Foundation's Kidney Disease and Outcomes Quality Initiative (Hogg *et al.,* 2003) have defined five stages

of CKD on the basis of different ranges of GFR: stage 1 GFR > 90 ml/minute/1.73 m^2 , stage 2 GFR 60 to 89 ml/minute/1.73m^2 , stage 3 GFR 30 to 59 ml/minute/1.73 m^2 , stage 4 GFR 15 to 29 ml/minute/1.73m^2 , and stage 5 GFR < 15 ml/minute/ 1.73 m^2.

As mentioned above, it has been suggested that periodontitis could be a non traditional risk factor for chronic kidney disease due to two factors. First, the systemic inflammatory burden caused by periodontal inflammation and its locally produced inflammatory mediators such as IL-1, IL-6, PGE2 and TNF alpha, and secondly, the presence of bacteria and their products in the blood stream. Paraveskas *et al.,* 2008, performed a systematic review and meta analysis on C-reactive protein in relation to periodontitis and discovered the majority of studies showed that CRP levels (>2.1mg/L) are elevated in periodontitis patients compared to controls. A meta analysis of 10 cross sectional studies revealed a weighted mean difference (WMD) of 1.56mg/L of CRP between patients and controls. It also showed a weighted mean difference in reduction of CRP after periodontal therapy of 0.50 mg/L. An investigation by Noack *et al.,* 2001 showed that elevated blood plasma levels of CRP were found in individuals with severe periodontal attachment loss compared to those with minimal to no attachment loss. This study reported that those infected with periodontal pathogens (*Porphyromonas Gingivalis, Prevotella Intermedia, Campylobacter recta, and Taneralla Forsythia*) had clearly higher levels of CRP than those not harboring the selected periodontal pathogens in their subgingival plaque. Another study by Kshirsager *et al.,* 2007 used the data from the Dental Atherosclerosis Risk in Communities study to investigate if there was a relationship between the presence of periodontal pathogens in the serum and kidney disease. They found that high serum levels of IgG to periodontal pathogens such as *Porphyromonas gingivalis, Treponema denticola*

and Aggregobacter actinomycetemcomitans were associated with an increased odds ratio of 1.6 to 1.8 for GFR < 60 ml/minute/1.73m^2, which they defined as kidney disease. In this study, estimates were adjusted for a wide range of confounders including age, race, sex, smoking, hypertension, body mass index (BMI) and education.

A few recent studies have found that patients with significant periodontal disease were 1.5-2 fold more likely to have CKD than those without periodontal disease. It is therefore the aim of this study to determine if, in a chronic kidney disease cohort, is there a correlation with periodontal disease using systemic markers such as eGFR, serum albumin to creatinine ratio %, and HbA1c.

METHODS AND MATERIALS

After approval by the Institution Review Board for research on human subjects and informed consent, a preliminary screening for potential subjects was conducted on patient data in the THREDS database by Dr. Vanessa Grubbs. In order for the patient to pass the initial screening process, they had to meet the following *inclusion criteria*: 1) Age 20 to 75 years; 2) Speaks English or Spanish; 3) At least 2 estimated glomerular filtration (eGFR) rate measurements of 15-59 mL/min/1.73 m^2 within the preceding 12 months; 4) No eGFR increase by ≥ 50% in the preceding 6 months; 5) Moderate/severe periodontal disease in accordance with the Centers for Disease Control and Prevention/American Academy of Periodontology definition AND at least 30% sites with bleeding on probing. The following was used as *general exclusion criteria*: 1) Under age 20 or over age 75; 2) Unable to understand and provide informed consent; 3) Currently receiving dialysis; 4) Receiving current immunosuppressant therapy; 5) Receiving current anticoagulation

therapy resulting in elevated prothrombin time or an International Normalized Ratio (INR) greater than 2.0; 6) Pregnant. The following was used as *oral exclusion criteria*: 1) Have fewer than 6 natural teeth; 2) Requires antibiotic prophylaxis for dental procedures as defined by the 2007 American Heart Association guidelines (patients with prosthetic heart valves, those with prosthetic material used for cardiac valve repair, those who have had a history of infective endocarditis, or those with congenital heart defects repaired with prosthetic material); 3) Have severe dental disease defined as deep dental caries, endodontic involvement of one or more teeth, presence of abscesses of periodontal or endodontic origin, or dental conditions requiring immediate treatment; 4) Have any hard or soft tissue lesion requiring further evaluation and/or treatment; 5) Have known allergy to minocycline, tetracyclines, or polyglycolate polymers.

Once patients passed the preliminary screening process, the oral screening examination was conducted in the Renal Clinic at SFGH by Dr. Mark Ryder (MR) or Periodontology Residents (PR) using a portable dental chair. Oral examination includes determination of: 1) Probing Depth (PD) - the distance from the free gingiva to the bottom of the gingival sulcus using a UNC probe; 2) Clinical Attachment Level (CAL) at 6 sites per tooth (DB, B, MB, DL, L, ML) - calculated as the sum of the distance from the CEJ to free gingival margin and probing depth; 3) assessment of Bleeding on Probing (BOP); 4) Plaque Index (Loe and Silness 1963); 5) Gingival Index (Silness and Loe 1964); 6) Preliminary determination of hopeless teeth that will be extracted at baseline (viability of suspect hopeless teeth was subsequently confirmed with a Panorex radiograph). MR calibrated all oral examiners to ensure inter-examiner validity.

Subjects who meet oral study criteria and CDC/AAP definition for moderate/severe periodontal disease were randomized 2:1 to either an intensive intervention cohort or a rescue treatment cohort in blocks of 3, with stratification by presence of diabetes to ensure balance between groups, during the baseline visit. Moderate periodontal disease was defined as ≥2 interproximal sites with CAL ≥4 mm (not on same tooth); OR ≥2 interproximal sites with PD ≥5 mm (not on same tooth) and severe periodontal disease was defined as ≥2 interpromixal sites with CAL ≥6 mm (not on same tooth) and ≥1 interproximal site with PD ≥5 mm, as shown in Table 1 (Eke *et al.,* 2012). This is an unblinded, randomized, controlled pilot trial with 2 intent-to-treat treatment arms: immediate intensive periodontal therapy or delayed intensive periodontal therapy. The study treatment and groups are summarized below:

Intensive Intervention Group: Subjects had scaling and root planing (deep cleaning removal of all gum disease), administration of Arestin to deeper gum pockets (of 5 mm or more), and extraction of hopeless teeth at the baseline study visit. Those with 2 or more quadrants affected with significant periodontal disease may be scheduled for a follow-up visit within 2 weeks for remainder of treatment. Additional deep cleaning and Arestin administration into the gingival sulcus will occur at months 4 and 8 as needed for persistent gum disease defined as any probing depth ≥5mm.

Rescue Treatment Group: Hopeless teeth were extracted (2 or more quadrants affected might have required a follow-up visit), but subjects would not undergo the intensive deep cleaning removal of plaque / treatment of gum disease, nor the administration of Arestin to deeper gum pockets at the beginning of the study. Subjects in the Rescue Treatment Group had these treatments at the end of the study (month 12).

Subjects were provided the Rescue Group Assignment Notification form and a handout referring them to local dental clinics. Rescue Treatment Group subjects that elected to receive outside dental treatment were not withdrawn from the study, but were asked about any outside treatment as part of the Follow-Up Questionnaire. Deep cleaning will occurred at baseline and at months 4 and 8 only for those teeth that had progressed 3 mm or more in probing depth since screening or the prior visit.

All Subjects: A baseline evaluation including dental measures was done and "hopeless teeth" were extracted. At the 4-, 8-, and 12-month visits, teeth that had progressed to hopeless were extracted. Subjects who had teeth extracted were provided with extraction aftercare instructions. Subjects received American Dental Association (ADA) handouts with instructions on dental hygiene ("How to Brush" and "How to Floss").

Table 1. CDC/AAP case definitions for periodontal disease

Case	Definition
No Periodontitis	No evidence of mild, moderate or severe periodontitis
Mild Periodontitis	≥ 2 interproximal sites with ≥ 3mm CA loss and ≥ 2 interproximal sites with ≥ 4 mm pocket depth (not on same tooth) or 1 site with ≥ 5 mm PD
Moderate Periodontitis	≥2 interproximal sites with CA loss ≥ 4 mm (not on same tooth); OR ≥ 2 interproximal sites with PD ≥ 5 mm (not on same tooth)
Severe Periodontitis	≥2 interpromixal sites with CA loss ≥ 6 mm (not on same tooth) and ≥ 1 interproximal site with PD ≥ 5 mm

Hopeless teeth were defined as those with 2 or more of the following: 1) Loss of over 75% of the supporting bone; 2) Probing depths greater than 8mm; 3) Class 3 furcation involvement; 4) Class 3 mobility with tooth movement in mesiodistal and vertical directions; 5) Poor crown to root ratio; 6) Root proximity with minimal bone and

evidence of horizontal bone loss. Hopeless teeth were determined by MR or PR (Periodontology Residents), and confirmed based on Panorex X-rays at baseline visit and, if clincially necessary, at the subsequent 4-, 8-, and/or 12-month study visits. Extractions of hopeless teeth were performed by PR at the UCSF Dental School using standard of care procedures, including collection of clinical consent for extractions. For subject comfort or if hopeless teeth were present in 2 or more quadrants, the extractions occurred on 2 separate days but within the subsequent 14 days. Any complicated extractions that could not be safely performed by PR were referred to the SFGH Oral Surgery Clinic. For visits requiring referral to the SFGH Oral Surgery Clinic, the Oral and Maxillofacial Surgery Patient Evaluation Form was completed to document medical status and medical history and the extraction treatment plan was described on the form. Due to availability of resources and/or staff complicated extractions actually occurred within the following 30 days. Blood and urine samples were collected at months baseline, 4, and 12, to assess variability in renal biomarkers and biomarkers of systemic inflammation, for all subjects. Women of childbearing age were asked to provide a urine sample for urine pregnancy test. Women who had a positive pregnancy test were not be given Arestin and were followed for outcomes of pregnancy and birth.

At baseline and every study visit, MR/PR will conducted a complete oral examination in the SFGH Oral Surgery Clinic including determination of PD and CAL at 6 sites per tooth, assessment of BOP, Plaque Index, Gingival Index, and determination of hopeless teeth. Per standard of care, confirmation that teeth were hopeless were on the basis of a Panorex radiograph performed for that purpose. Saliva, subgingival plaque, and gingival crevicular fluid (GCF) were collected from all subjects during the baseline visit oral

examination and at the 12-month study visit. During this baseline study visit, all subjects completed study coordinator administered questionnaires [Baseline Questionnaire; the reading comprehension questionnaire entitled "Short Test of Functional Literacy in Adults" (STOFHLA); and the Adverse Events Form], underwent basic physical examination (including height, weight, and blood pressure measurement) and phlebotomy. Women of childbearing age provided a urine sample to be tested for pregnancy. These procedures took place in the SFGH Clinical Research Services Unit. The blood samples were evaluated for levels of:

Creatinine

Neutrophil gelatinase-associated lipocalin (NGAL, a marker of renal tubular injury)

Assymetrical dimethylargine (ADMA, a marker of endothelial injury)

Interleukin 6 (IL-6, a biomarker of systemic inflammation)

C-reactive protein (CRP, a biomarker of systemic inflammation)

Cotinine (a metabolite of nicotine and biomarker for exposure to tobacco smoke)

Hemoglobin A1c (HbA1c, a marker for diabetes)

Serum cystatin C

The following tests were performed on the urine samples:

Protein levels

NGAL

Cotinine

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol [NNAL, a metabolite of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and biomarker for tobacco use]

Once all diagnostic data had been collected at baseline visit, hopeless teeth were extracted at baseline for all subjects. Those assigned to the Intensive Intervention Group underwent intensive treatment to include administration of local anesthetic to up to 2 oral quadrants for scaling and root planing with ultrasonic and hand instruments. Arestin (minocycline HCl) was applied to any sites with probing depth ≥ 5 mm. Women with positive urine pregnancy tests (*i.e.*, have become pregnant while on-study) who were assigned to the Intervention Group did not receive Arestin. Subjects assigned to the Rescue Treatment Group underwent assessment and documentation of the levels of periodontal disease throughout the oral cavity. They had extraction of hopeless teeth plus scaling and root planing only to sites of disease progression (3 mm or more) since screening examination. If any subjects indicated concern about waiting until end of study for full intensive treatment, they were reminded that they could choose to receive additional dental care outside of the study. All subjects were given an appointment for the 4-month study visit and instructions to bring with them all medications and bottles (including dietary supplements). The subjects were provided with a sample receptacle for a first morning voided urine sample to be collected on the morning of the study visit.

At the 4-month study visit, all subjects completed study coordinator administered questionnaires to assess interim medical and dental history and adverse events (Study Visit

Follow-up Questionnaire and Adverse Events Form); and underwent basic physical examination (including height, weight, and blood pressure measurement) and phlebotomy (creatinine; NGAL; ADMA; IL-6; Creactive protein; HbA1c; and serum cystatin C), and a dental evaluation. Urine samples were collected for quantification of albuminuria and NGAL. Women of childbearing age had urine tested for pregnancy. Women with positive urine pregnancy tests (*i.e.*, had become pregnant while on-study) who were assigned to the Intervention Group did not receive Arestin. These procedures took place in the SFGH Clinical Research Services Unit. If any teeth at this visit were deemed hopeless according to the diagnostic criteria outlined in the baseline visit, they were extracted following the same protocols outlined in the baseline visit. Subjects assigned to the Intensive Intervention Group underwent repeated scaling and root planing; plus administration of Arestin to sites of persistent disease (5 mm or more probing depth) after administration of local anesthetic. Subjects assigned to the Rescue Treatment Group received rescue scaling and root planing only to sites of disease progression (since prior examination) of greater than 3 mm after administration of local anesthetic. Subjects assigned to the Rescue Treatment Group did not receive Arestin at this visit. All subjects were given an appointment for the 8-month study visit and instructions to bring with them all medications and bottles (including dietary supplements). The subjects were provided with a sample receptacle for a first morning voided urine sample which was collected on the morning of the study visit.

The 8-month study visit was the same as those for the 4-month study visit except that there was no phlebotomy. If any teeth at this visit were deemed hopeless according to the diagnostic criteria outlined in the baseline visit, they were extracted following the same protocols outlined in the baseline visit. All subjects were given an appointment for the 12-

month study visit and instructions to bring with them all medications and bottles (including dietary supplements). The subjects were provided with a sample receptacle for a first morning voided urine sample to be collected on the morning of the study visit.

At the 12-month study visit, all subjects completed the study coordinator-administered questionnaires (Adverse Events, Study Visit Follow-up Questionnaire, and the End-of-Study Questionnaire); and underwent basic physical examination (including height, weight, and blood pressure measurement) and phlebotomy (creatinine; NGAL; ADMA; IL-6; Creactive protein; HbA1c; and serum cystatin C). Urine samples were collected for quantification of albuminuria and NGAL. Women of childbearing age had urine tested for pregnancy. Women with positive urine pregnancy tests (*i.e.*, had become pregnant while on the study) who were assigned to the Intervention Group did not receive Arestin. These procedures took place in the SFGH Clinical Research Services Unit. If any teeth at this visit were deemed hopeless according to the diagnostic criteria outlined in the baseline visit, they were extracted following the same protocols outlined in the baseline visit. Subjects assigned to the Intensive Intervention Group will underwent rescue scaling and root planing only to sites of disease progression (since prior examination) of greater than 3 mm after administration of local anesthetic. Subjects assigned to the Rescue Treatment Group underwent intensive treatment to include administration of local anesthetic to up to 2 quadrants for scaling and root planing with ultrasonic and hand instruments. Those who had more than 2 quadrants affected with significant periodontal disease were scheduled for a follow-up visit within 2 weeks for remainder of treatment. Arestin (minocycline HCL) was applied to any sites with probing depth ≥ 5 mm. Women with positive urine pregnancy tests (*i.e.*, had become pregnant while on study) did not receive Arestin.

RESULTS

After applying the inclusion and exclusion criteria for kidney and periodontal parameters as stated above, 21 participants met our study requirements and entered the study. Patient characteristics by CKD values are shown in Table 2.

Table 2. Patients characteristics by CKD values

Participant ID	Event Name	eGFR	HbA1c (%)	Albumin to creatinine ratio (%)
140	Baseline Visit	46	5.6	<9.3
213	Baseline Visit	39	5.3	<3.2
225	Baseline Visit	32	6.4	317.9
326	Baseline Visit	44	5	36.7
357	Baseline Visit	30	5.7	57.6
363	Baseline Visit	46	5.6	<13.8
449	Baseline Visit	41	5.9	34
569	Baseline Visit	52	8.4	1264.9
601	Baseline Visit	45	6.9	565.7
641	Baseline Visit	37	6	3040.6
758	Baseline Visit	30	6.6	89.4
803	Baseline Visit	56	5.7	<6.0
832	Baseline Visit	54	5.9	157.3
975	Baseline Visit	41	5.7	<5.3
1020	Baseline Visit	57	9.2	471.8
1227	Baseline Visit	30	8.8	409.6
1320	Baseline Visit	41	6	167.8
1459	Baseline Visit	60	6.8	<2.4
1554	Baseline Visit	43	7.7	21.8
1596	Baseline Visit	24	6.5	24
1612	Baseline Visit	53	7.2	<3.7

Patients eGFR values were all <60 ml/min/m^2 , but above >15 ml/min/m^2 which means patients' were diagnosed with chronic kidney disease, but were not in kidney failure. Patients' HbA1c % values ranged from 5 to 9.2. Patients' serum albumin to creatinine %

ratio ranged from 2.4 to 3040.6. Patient characteristics by periodontal parameters are shown in Table 3.

Table 3. Patient characteristics by periodontal parameters

Participant ID	Average PD	Average CAL	% BOP	Average GI	Average PI
140	3.63	0.03	45.37	1.54	1.36
213	2.86	1.83	75.00	1.53	1.73
225	3.23	3.25	70.83	1.87	1.40
326	2.74	3.23	70.00	1.80	1.50
357	4.64	5.94	75.93	2.35	1.63
363	3.49	3.73	59.52	1.56	1.43
449	2.81	3.40	55.95	1.14	0.75
569	2.66	2.55	38.33	1.01	0.77
601	3.45	3.96	30.13	1.13	0.88
641	2.19	1.51	34.52	1.06	1.50
758	2.80	2.85	39.88	1.00	2.80
803	3.71	4.06	85.19	2.43	1.56
832	3.44	4.85	61.11	2.21	1.57
975	3.45	2.75	95.68	2.00	1.13
1020	4.54	4.45	96.00	1.65	1.20
1227	3.64	3.77	73.96	2.21	1.09
1320	2.88	3.42	34.48	1.11	1.00
1459	3.78	4.89	37.33	1.28	1.54
1554	2.91	1.74	39.51	0.97	0.41
1596	3.71	2.36	48.15	*1.14	1.20
1612	3.27	4.57	62.28	1.57	0.79

Average study values of entire study population are included in table 4.

Table 4. Simple statistics of entire population

Label	Mean	Std Dev	Median
eGFR	42.90	10.08	43.00
HbA1c %	6.52	1.16	6.00
Albumin to creatinine ratio %	475.65	811.32	162.55
Average PD	3.32	0.60	3.44
Average CAL	3.45	1.13	3.40
% BOP	58.53	20.53	59.52
Average GI	1.55	0.48	1.54
Average PI	1.30	0.49	1.36

The average eGFR of our entire study population was 42.9 and the average HbA1c was 6.51. The average serum albumin to creatinine ratio % was 475.65. The patient population also had an average probing depth of 3.32 mm, CAL of 3.44 mm, and BOP of 58%.

For correlation between kidney markers and periodontal markers, a Spearman correlation coefficient was calculated. Of note, we found that eGFR was moderately positively correlated with average CAL (r coefficient = 0.46956, p value=0.0317) as seen in Figure 1.

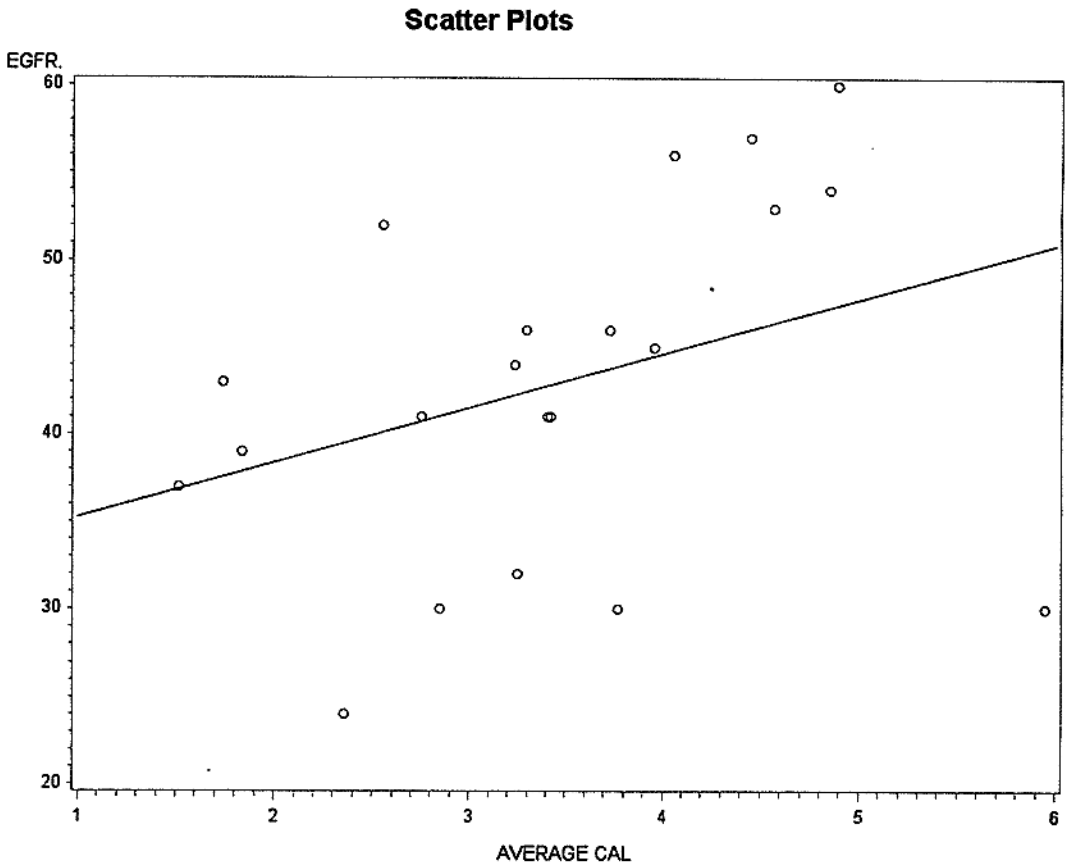

Fig 1. Spearman correlation coefficient comparing average CAL to eGFR (r = 0.46956, p value=0.0317).

Additionally, HbA1c(%) was moderately negatively associated with average PI (r =

coefficient -0.51205, p value=0.0176) as seen in Figure 2.

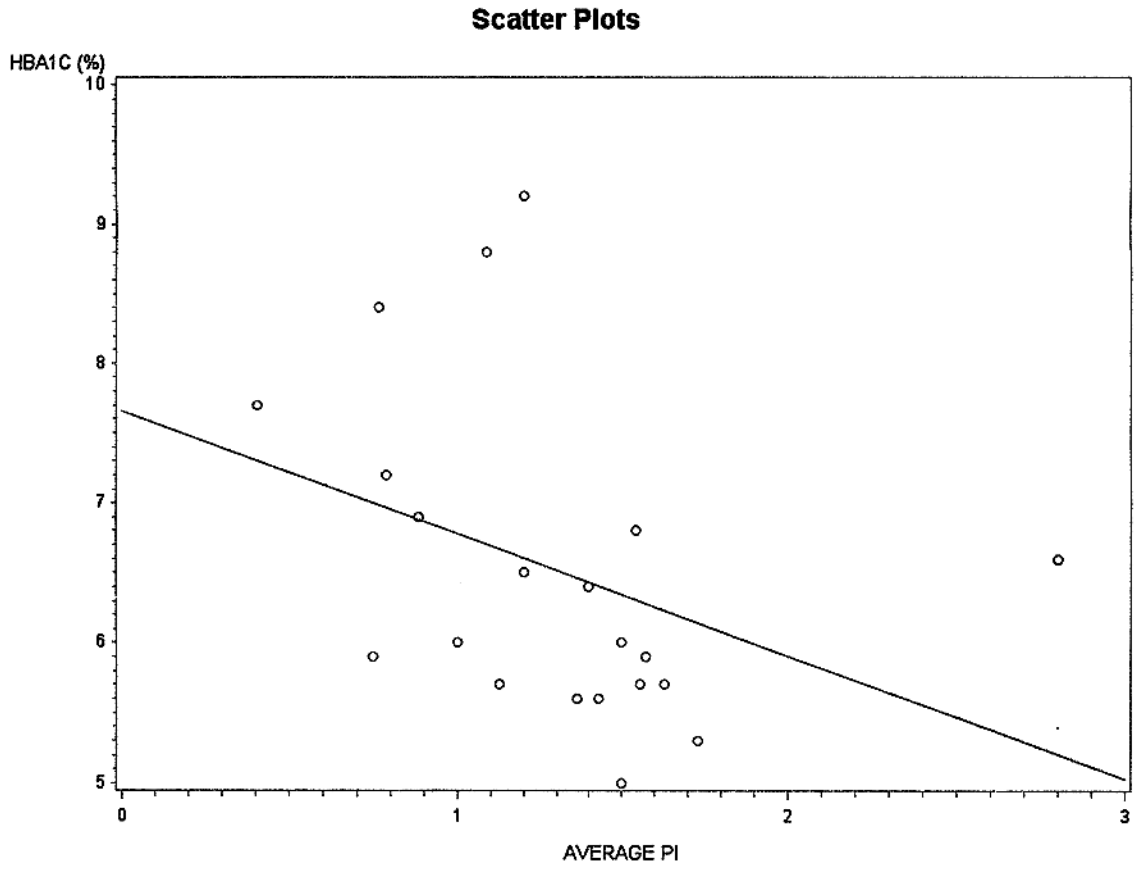

Fig 2. Spearman correlation coefficient comparing average PI to HbA1c% (r = coefficient -0.51205, p value=0.0176).

The periodontal markers such as PD and CAL were stratified into categories and analyzed for correlations between kidney markers such as eGFR, HbA1c, and serum albumin to creatinine ratio %. Patients' with CAL from 0-2mm had an average eGFR or 39.66 and patients' with CAL of 5+mm had an average eGFR of 30.0 but was not statistically significant. This data is presented in Table 5.

Table 5. Average CAL stratified into categories compared with kidney markers

Avg CAL (mm)	N Obs	Label	N	Mean	Std Dev	Minimum	Maximum
0-2	**3**	**EGFR.**	3	39.6666667	3.0550505	37	43
		HBA1C (%)	3	6.3333333	1.2342339	5.3	7.7
		ALBUMIN TO CREATININE RATIO (%)	2	1531.2	2134.61	21.8	3040.6
2.1-4.9	**17**	**EGFR.**	17	44.2352941	10.5624891	24	60
		HBA1C (%)	17	6.6	1.1963486	5	9.2
		ALBUMIN TO CREATININE RATIO (%)	11	321.7363636	365.6132554	24	1264.9
5+	**1**	**EGFR.**	1	30	.	30	30
		HBA1C (%)	1	5.7	.	5.7	5.7
		ALBUMIN TO CREATININE RATIO (%)	1	57.6	.	57.6	57.6

When the probing depth data was stratified into categories, patients' with an average PD of 0-3mm had an average HbA1c % of 6.36 and patients' with an average PD of 3+mm had an average HbA1c % of 6.61. However, the difference in HbA1c levels were not statistically significant. This data is presented in Table 6.

Table 6. Average PD stratified into categories compared with kidney markers

Avg PD (mm)	N Obs	Label	N	Mean	Std Dev	Minimum	Maximum
0-3	**8**	**EGFR.**	8	40.875	6.266407	30	52
		HBA1C (%)	8	6.3625	1.1624328	5	8.4
		ALBUMIN TO CREATININE RATIO (%)	7	665.0285714	1139.34	21.8	3040.6
≥3.1	**13**	**EGFR.**	13	44.1538462	11.9152994	24	60
		HBA1C (%)	13	6.6153846	1.1922291	5.6	9.2
		ALBUMIN TO CREATININE RATIO (%)	7	286.2714286	210.7217891	24	565.7

There was no statistically significant correlation between BOP % and markers of kidney function assessed in this study such as eGFR, HbA1c, and serum albumin to creatinine ratio %.

DISCUSSION

Since the association between periodontal disease and chronic kidney disease is in its early stages of investigation, there are currently no large-scale epidemiologic studies comparing the oral health status in patients with chronic kidney disease and control patients with normal renal function. There are, however, several smaller studies providing evidence to suggest that there may be a link between periodontal disease and chronic kidney disease. Kshirsagar *et al.,* 2005 conducted a cross-sectional study of 5,537 middle-aged black and white men and

women. They found 110 individuals (2%) had a GFR less than 60 mL/min/1.73 m^2. Compared with healthy/gingivitis, initial and severe periodontal disease were associated with a GFR less than 60 mL/min/1.73 m^2 (odds ratio, 2.00; 95% confidence interval, 1.23 to 3.24) for initial periodontal disease and an odds ratio of 2.14 for severe disease (95% confidence interval, 1.19 to 3.85) after adjustment for important risk factors for CVD and CKD. This was the first study to show an association of periodontal disease with prevalent renal insufficiency. Another study by Davidovich *et al.,* 2005, examined four renal failure groups: chronic renal disease (n=22); undergoing dialysis (n=22); after dialysis and transplant (n=21); and after transplant (n=32), and compared them to a healthy control (n=38). The renal failure groups had higher gingival index (GI) and bleeding, probing depths, and attachment loss compared to healthy renal groups. Dialysis duration and end-stage renal failure patients were significantly correlated with increased gingivitis, probing depth, and attachment loss. Shultis *et al.,* 2007 observed individuals in the Gila River Indian Community to determine if there was an association between periodontitis and chronic kidney disease in type 2 diabetic patients. Age- and sex-adjusted incidence of macroalbuminuria and ESRD increased with severity of periodontitis. Incidences of ESRD in individuals with moderate or severe periodontitis or in those who were edentulous were 2.3, 3.5, and 4.9 times as high, respectively, compared with those with none/mild periodontitis (p=0.02). Additionally, Borawski *et al.,* 2007, compared 106 dialysis and CKD subjects to a group of 26 generally healthy individuals with advanced periodontitis and another group of 30 subjects from the general population. Their results indicated a higher severity of periodontitis in all renal failure groups as compared with general population subjects. Fischer *et al.,* 2009 analyzed data of individuals >18 years of age who had a

periodontal examination from NHANES III. She discovered that periodontitis was associated with an increased odds ratio of 1.6 in CKD patients. Furthermore, Fischer *et al.,* 2011, used structural equation modeling to suggest that periodontal disease was independently associated with CKD in a bidirectional relationship mediated by diabetes duration hypertension. Grubbs *et al.,* 2011 looked at data from 2001 to 2004 in NHANES and found that Periodontal disease was associated with >2-fold higher risk of CKD. After adjusting for age, gender, race/ethnicity, tobacco use, hypertension, diabetes, educational attainment, poverty index ratio, and dental care use there was still a 51% increased odds (95% CI 13%–102%) of CKD associated with moderate and severe periodontal disease. Another study by Ioannidou *et al.,* 2011 used the data from NHANES III and stratified the data by race and ethnicity to determine if chronic kidney disease (CKD) patients would have higher prevalence of moderate periodontitis compared with individuals without CKD. Overall, 14.6% of individuals with CKD were classified as having moderate periodontitis, compared with 8.7% in the non-CKD group ($p = 0.001$). A significant dose response association ($p = 0.001$) was observed between prevalence of moderate periodontitis and CKD stages among non-Hispanic Blacks and Mexican-Americans, but not so for non-Hispanic Whites. Prevalence of periodontitis among participants with CKD was substantially higher among non-Hispanic Blacks (38.9%) and Mexican-Americans (37.3%) compared with non-Hispanic Whites (12.9%). Multivariate logistic regression models showed that Mexican-Americans and non-

Hispanic Blacks with CKD were approximately 30% to 60% more likely to have moderate periodontitis compared with those without CKD, after adjustment for diabetes status and other potential confounders.

Although there is an increasing amount of evidence suggesting the association between periodontal disease and chronic kidney disease, not all studies can confirm this positive association. For example, an investigation by Castillo *et al.,* 2007 performed a cross sectional study to evaluate the periodontal status and oral microbiological patterns of a population with end-stage renal disease (ESRD), undergoing haemodialysis (HD). No statistically significant differences were found between the HD patients and the control group regarding bleeding index, number of teeth, or percentage of loss of periodontal attachment >3 mm. Although HD patients presented a higher number of periodontopathic microorganisms than the matched controls, a prolonged duration of HD did not bear a statistically significant relationship with the percentage of sites with loss of periodontal attachment >3 mm, specific microbiota or composition of biofilm.

Our study seems to be in the minority and agree with the study by Castillo *et al.,* 2007 in that there is no correlation between the severity of periodontal disease and the severity of chronic kidney disease. There were a few specific findings in our study that would seem counterintuitive. First, we found that there was a moderately positive correlation with eGFR and average CAL. This would seem to suggest that as one of the surrogate markers for periodontal disease, CAL, increased, the function of the kidneys improved as measured by eGFR. A systematic review by Chambrone *et al.,* 2013, stated, "there is quite secure evidence to support the positive association between periodontitis and CKD". The group went even further by saying the accumulated evidence suggests that improvement of periodontal parameters through periodontal therapy seems to increase eGFR. However, they also noted it was also not possible to confidently sustain the hypothesis that periodontal therapy could improve eGFR due to the lack of RCTs. Second,

our study found that HbA1c(%), a marker for longer term glycemic control, was moderately negatively associated with average PI. This suggests that as a surrogate marker for inflammatory burden, plaque index increased, patients blood glucose control improved, or their HbA1c levels decreased. This is contradictory to most evidence out there currently. Taylor *et al.*, 2006, performed a 2-year longitudinal trial and found that diabetic subjects with severe periodontitis at baseline had a six-fold increased risk of worsening of glycemic control over time compared to diabetic subjects without periodontitis. However, a systematic review performed by Borgnakke *et al.*, 2013, cautions that the "current evidence for effects of periodontal disease on glycemic control is scarce." They do note that compared to periodontally healthy individuals, people with poor periodontal health and type 2 diabetes have greater risk for developing poorer glycemic control.

However, our study has a few limitations that need to be noted. First, our study is a pilot study and had a small population, so conclusions drawn from this data should be interpreted with caution. Additionally, patients were drawn from the SFGH database and had to speak either English or Spanish, so this may not be a population representative of the general population.

Since it seems there is a larger body of evidence to suggest that periodontal disease may be a risk factor for chronic kidney disease, the next issue to address would be if periodontal therapy improves the prognosis or outlook of markers of CKD. An investigation by Chambrone *et al.*, 2013 performed a systematic review of studies analyzing the effect of periodontal treatment on chronic kidney disease or its surrogate outcome, estimated glomerular filtration rate. They identified 2456 potentially eligible articles, of which four cross sectional, one retrospective, and three interventional studies

were included. Periodontal therapy was defined as scaling and root planing, supragingival debridement/tooth polishing, or scaling and root planing with systemic antibiotics. They found that the accumulated evidence from individual studies suggests that periodontal therapy seems to increase the estimated glomerular filtration rate. A small exploratory study by Graziani *et al.,* 2010 looked at twenty systemically healthy patients with generalized chronic periodontitis who underwent non surgical periodontal therapy. Baseline and final periodontal outcome measures showed statistically significant improvements of all clinical parameters and levels of cystatin C (an important marker of eGFR) can be decreased following periodontal therapy in this patient population. Another study by Artese *et al.,* 2010 investigated the effect of non-surgical periodontal therapy on chronic kidney disease patients. Twenty-one predialysis patients (group 1) and 19 individuals without clinical evidence of kidney disease (group 2) with chronic periodontitis were subjected to scaling and root planing without antibiotics. Clinical periodontal and systemic parameters were evaluated at baseline and 3 months after treatment. Both groups showed significant and similar post-treatment improvements in all periodontal parameters examined. Additionally, periodontal treatment had a statistically significant positive effect on the glomerular filtration rate of each individual (group 1, $p = 0.04$; group 2, $p = 0.002$). Vilela *et al.,* 2011 included 56 chronic periodontitis patients, 36 of whom had chronic kidney disease and 20 of whom were systemically healthy and had normal renal function. The inflammatory markers ultrasensitive C-reactive protein, interleukin-6, and prohepcidin were evaluated before and 3 months after scaling and root planing. The efficacy of periodontal treatment was confirmed by the improvement in clinical parameters of chronic periodontitis in the control and chronic kidney disease

groups. Periodontal treatment resulted in significant reductions in ultrasensitive C-reactive protein, interleukin-6, and serum prohepcidin levels in both groups. None of these interventional studies reported the occurrence of adverse effects/complications related to periodontal therapy.

Conclusion

There was no evidence in this study that supported the hypothesis that the severity of periodontal disease is correlated to the severity of chronic kidney disease and vice versa. However, there is a multitude of studies that support the idea that periodontal disease is correlated with chronic kidney disease. The results of this study need to be interpreted with caution due to the small population (n = 21). This was intended to be a pilot study with a limited amount of time and finances. Therefore, larger scale studies with more subjects, which look at populations more representative of the population as a whole, need to be conducted to determine if there is a correlation between periodontal disease and CKD. Also, longitudinal studies of this magnitude need to be carried out to see if improvements of markers of one disease affect markers of the other to truly determine if correlation exists between the two disease entities.

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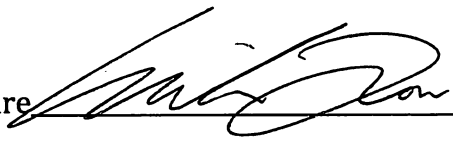
Author Signature  Date 6/12/15