Title
In a Population of Patients with Compromised Renal Function, Is There a Difference in Periodontal Outcomes between the Intensive Intervention vs. Community Treatment Group?

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In a Population of Patients with Compromised Renal Function, Is There a Difference in Periodontal Outcomes between the Intensive Intervention vs. Community Treatment Group?

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THESIS

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DEDICATION

I would like to dedicate this Master's Thesis to all the wonderful faculty and friends at the University of San Francisco that have made the last seven years a memorable experience. I will truly miss your wisdom and friendship I so sought.

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In a Population of Patients with Compromised Renal Function, Is There a Difference in Periodontal Outcomes between the Intensive Intervention vs. Community Treatment Group?

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ABSTRACT

Introduction: It has been suggested in the literature that a bidirectional relationship exists between periodontal disease and Chronic Kidney Disease (CKD), which in turn, modifies the host's ability to manage and respond to punitive periodontal pathogens. The objective of this study was to determine if there is a difference in periodontal outcomes between non-surgically treated CKD patients with periodontal disease and those with the disease who did not obtain treatment.

Materials and Methods: This is an un-blinded, randomized, controlled pilot trial with two intent-to-treat treatment arms: intensive intervention (INT) group, which obtained non-surgical periodontal treatment with local delivery of Arestin at baseline and at four months, and the community treatment (CT) group, which did not receive periodontal intervention until the end of the study. All subjects had a history of periodontal disease and identified as having compromised renal function if they presented with at least two estimated glomerular filtration (eGFR) rate measurements of 15-59 mL/min/1.73 m within the preceding 12 months.

Results: 12 subjects from the San Francisco General Hospital Renal Clinic have completed the study. All sites within the treatment intervention group showed that there were significant changes in average pocket depth (PD) (0.82mm reduction, p=0.0078), percent bleeding on probing (BOP) (28% reduction, p=0.0078), and gingival index (GI) (0.78 reduction, p=0.0078) at four months compared to baseline. Intergroup comparison from baseline to four months demonstrated that the treatment group had significantly different average GI change at all sites than the control group (treatment: 0.78 average reduction, control: 0.06

average reduction, p=0.0283) and marginally significantly different percent BOP change for all sites than the control group (treatment: 28% average reduction, control: 2% average increase, p=0.0727).

Conclusion: Our results showed that the intensive intervention groups experienced a significant improvement in the periodontal parameters measured (PD, BOP, clinical attachment level (CAL), and GI). Additionally, BOP and GI improved statistically when compared between groups. Given the demonstrated potential benefits of non-surgical periodontal therapy, longitudinal studies should be completed to determine the bidirectional relationship as well as to assess the role of inflammation and its link to CKD and periodontal disease.

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INTRODUCTION

A current question in the field of periodontology is whether systemic diseases can be affected by the progression and treatment of periodontitis. It is well documented in the literature that there is a relationship between oral bacteria and systemic diseases such as bacterial endocarditis, cardiovascular diseases, atherosclerosis, diabetes, and respiratory illness.[16] Several studies have set out to establish if the opposite is true and to determine whether there is a bidirectional relationship in inflammation caused by systemic disease that can be contributed to periodontal injury.[13] The relationship between chronic inflammation caused by Gram-negative bacteria in periodontal disease has not been well established as a risk factor for Chronic Kidney Disease (CKD). More difficult to determine is the opposite concept – if the chronic inflammation caused by CKD has a role in destruction of the periodontium.

The lifetime risk of CKD is high, with estimates more than half of U.S. adults aged 30 to 64 likely to develop CKD between the years 2020 to 2030. Chronic Kidney Disease is a major cause of morbidity and mortality, and is associated with high medical costs in the United States. It is estimated that one in seven adults has CKD and the number of deaths have doubled in the past two decades.[12] The progressive loss of renal function with CKD worsens over a period of months to years. The most recent guidelines classify the severity of the disease into five stages (Table 1), from the mildest form to the most severe form, which is Stage 5, or chronic kidney failure.[14]

Table 1. Stages of chronic kidney disease.

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15 (or dialysis)

Patients with chronic kidney failure usually require dialysis with the hope of renal replacement therapy. During this progression, patients are burdened by high medical fees and are at an increased risk of end stage renal disease, cardiovascular disease, and premature death.[9] Raising individual awareness of CKD may encourage people to take steps to prevent CKD. From a national prospective, if the prevalence of CKD is expected to increase in the coming decades, then steps need to be taken to identify and modify possible risk factors.

Many patients with CKD can experience oral symptoms that include gingival inflammation, gingival enlargement and attachment loss, alterations in salivary composition, reduced salivary flow rate, adverse effects related to drug therapy, mucosal lesions, oral malignancies, oral infections, dental anomalies, and bone lesions.[15] Increasing evidence from epidemiologic studies suggest an association between periodontal disease and CKD. Several studies have suggested that subjects with periodontal disease are 1.6-2 times more likely to have CKD than those without periodontal disease.[6-8, 11] It has also been suggested that chronic bacterial infection from periodontal disease result in a systemic inflammatory response that may add to the chronic inflammation present in CKD. The molecular and cellular mechanism suggested through these studies propose that circulating bacterial coating and byproducts can bind to specific receptors found throughout the kidney and activate a local inflammatory cascade that may lead to deterioration in renal function.[2, 3] It is important to take into consideration that CKD is an immunocompromised state characterized by impaired function of monocytes, macrophages, T- and B- cells.[9] For this reason, it can be presumed that patients with CKD may be ill equipped to initiate and manage an immune response to a periodontal infection.

It is the aim of this study to determine, as well as understand, if intensive periodontal intervention will have an effect on a population with periodontal disease and chronic kidney disease (CKD), as measured by periodontal outcomes.

MATERIALS AND METHODS

This is an unblinded, randomized, controlled pilot trial with an intent-to-treat treatment arm and a community treatment group which did not receive care within our clinic but was welcome to seek treatment outside our clinic during the course of the study. Funding for this study was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. The patient population comprised of patients with compromised renal function. These subjects were first screened with a questionnaire. Subjects who qualified and consented to enroll in the study were then given an appointment for the baseline study visit and instructions to bring with them all medications and bottles (including dietary supplements). At the baseline and 4 month visit all patients were evaluated for periodontal parameters including Probing Depth (PD), Clinical Attachment Level (CAL) at six sites per tooth, assessment of Bleeding on Probing (BOP), Plaque Index (PI), Gingival Index (GI), and preliminary determination of hopeless teeth that would be extracted at baseline. The original study design was to follow these patients for 12 months. Due to the difficulty to enroll subjects in a timely manner to complete the study, the data presented discusses the change in the periodontal parameters over a four month period.

Determining Sample Population

This is a pilot study and, to our knowledge, there is no existing data of the anticipated effect size of periodontal treatment to inform sample size calculations. However, because a portion and primary aim of this study was to determine the variability of various renal and inflammatory biomarkers, we sought to enroll at least 30 subjects in the intervention arm of the trial. We assumed 25% of patients screened would meet all inclusion/exclusion criteria and enroll in the study. Randomization was stratified with respect to diabetes (a strong risk factor for causing/aggravating both CKD and periodontal disease) to prevent an imbalance between the two arms. The accrual target was 51 patients from the San Francisco General Hospital (SFGH) Renal Clinic.

Exclusion/Inclusion Criteria

Patients were defined to have compromised renal function if they presented with at least two estimated glomerular filtration (eGFR) rate measurements of 15-59 mL/min/1.73 m within the preceding 12 months. Inclusion criteria for the study included an age requirement in which patients must be between 20 and 75 years of age. All patients were required to speak English or Spanish. Patients were excluded if there was an increase in eGFR by 50% or greater in the preceding six months. Moderate/severe periodontal disease was defined in accordance with the Centers for Disease Control and Prevention and the American Academy of Periodontology and required at least 30% sites with bleeding on probing.

Exclusion criteria included subjects who were younger than age 20 or older than age 75, unable to understand and provide informed consent, currently receiving dialysis, receiving current immunosuppressant therapy, receiving current anticoagulation therapy resulting in an elevated prothrombin time or an International Normalized Ratio (INR) greater than 2.0, or was pregnant. Patients who required 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) were excluded from the study. Additionally, patients who had a known allergy to minocycline, tetracyclines or polyglycolate polymers were also excluded from the study.

Baseline Oral Screening Exclusion Criteria

During the baseline oral examination, patients were examined for oral findings that could exclude them from the study. Exclusions included having fewer than six natural teeth; 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; and hard or soft tissue lesions requiring further evaluation and/or treatment. Hopeless teeth were defined as those with two or more of the following: (1) loss of more than 75% of the supporting bone; (2) probing depths >8 mm; (3) class III

furcation involvement; (4) class III mobility with tooth movement in mesial distal and vertical directions; (5) poor crown-root ratios; or (6) root proximity with minimal interproximal bone and evidence of horizontal bone loss. The viability of the suspected hopeless teeth were confirmed with a Panorex radiograph. All three residents were calibrated to ensure inter-examiner validity.

Randomization and Study Procedures

Subjects who met oral study criteria and CDC/AAP definition for moderate/severe periodontal disease were randomized 2:1 to either an intensive intervention cohort or a community treatment cohort in blocks of 3, with stratification by presence of diabetes to ensure balance between groups. The study treatment groups are summarized below.

All subjects were provided with a sample receptacle for a urine sample to be collected on the first morning of the study visit. Each subject completed a baseline evaluation including dental measures, and those with "hopeless" teeth had the teeth extracted. At the four-month visits, teeth that had progressed to hopeless were extracted. Subjects who had teeth extracted were provided with extraction aftercare instructions. All subjects received American Dental Association (ADA) handouts with instructions on dental hygiene. Extractions of hopeless teeth were performed by periodontology residents at the University of California, San Francisco (UCSF) Dental School using standard of care procedures, including collection of clinical consent for extractions. Any complicated extractions that could not be safely performed by the periodontology residents were referred to the SFGH Oral Surgery Clinic. At the conclusion of the study visit, each subject received compensation in the amount of $50 for their participation. Subjects who required extraction of hopeless teeth were compensated an additional $25.

Screening questionnaire

A screening questionnaire was completed with a study staff member in order to obtain medical and dental history, as well as to verbally review consent and criteria. Women of childbearing age were asked to provide a urine sample for a urine pregnancy test. Women with a positive pregnancy test were not included. Women

with a negative pregnancy test were instructed not to become pregnant during the study. Potential subjects who met the study criteria underwent further screening with an oral examination. Consented subjects who did not meet the criteria were considered "Screen Failures" and were subsequently exited from the study and provided with a written recommendation for needed care at exit or by mail.

Baseline Oral Screening

The oral screening examinations were conducted in the Renal Clinic by one of three UCSF Postgraduate Periodontology Residents using a portable dental chair. Periodontal outcome indices included determining Probing Depth (PD) and Clinical Attachment Level (CAL) at six sites per tooth, assessment of Bleeding on Probing (BOP), Plaque Index (PI), Gingival Index (GI), and preliminary determination of hopeless teeth that would be extracted at baseline.

Intensive Intervention Group

At baseline and at four months, all subjects received oral hygiene instructions, scaling and root planing with ultrasonic and hand instruments (Gracey curettes), and polishing under the administration of local anesthetic. Arestin (Minocycline Hydrochloride, OraPharma, Horsham, PA) was administered to deeper pockets (>5 mm), and hopeless teeth were extracted.

Community Treatment Group

Hopeless teeth were extracted, but subjects did not undergo the intensive deep cleaning removal of plaque and calculus to treat gum disease, nor the administration of Arestin to deeper gum pockets at the beginning of the study. Subjects in the Community Treatment Group, instead, received these treatments at the end of the study. Subjects were provided the Community Group Assignment Notification form and a handout referring them to local dental clinics. Community Treatment Group subjects that elected to receive outside dental treatment were not withdrawn from the study, but were asked about any outside treatment they received as part of a follow-up questionnaire.

Collection of Biologic Samples

For all subjects, blood and urine samples were collected at baseline and at four months to assess variability in renal biomarkers and biomarkers of systemic inflammation for a segment of the study to be completed separately. Women of childbearing age were asked to provide a urine sample for urine pregnancy test. Women with a positive pregnancy test were not given Arestin and were followed for outcomes of pregnancy and birth.

Blood samples were evaluated for levels of: Creatinine Neutrophil gelatinase-associated lipocalin (NGAL, a marker of renal tubular injury) Hemoglobin A1c (HbA1c, a marker for diabetes. Urine samples were collected for quantification of albuminuria and NGAL.

Statistical Analysis

Signed rank test for pre- and post-comparison were completed within each group to compare significant changes in pocket depth (PD), clinical attachment loss (CAL), bleeding on probing (BOP), gingival index (GI), plaque index (PI), HBA1c and Albumin Creatinine (AC). Exact Wilcoxon rank sum test was also completed for intergroup comparison of the baseline and 4-month change in HBA1C and AC, and periodontal parameters. Spearman correlation coefficients were estimated between change in periodontal parameters and change in kidney functions with all available data. The results were considered statistically significant at a $p < 0.05$.

RESULTS

Demographics

Table 2 provides the demographic features of the population. Forty-nine patients were initially screened for the study, of which 20 subjects were enrolled. The following data represents the 12 of 20 individuals who have completed the four-month follow-up visit at this point of the study. Of those 12 individuals, eight subjects were randomized to the INT group and the remaining four were placed in the CT group. All four subjects in the CT group were males (100%). One female was enrolled in the INT group (12.5%). The

average age of the INT and CT groups were 61.5+/-4.7 and 59 +/- 9.9, respectively. A majority of the patients did not report their ethnicity; therefore, demographic analysis of ethnicity could not be completed. Two of the four (50%) subjects in the CT group and four out of the eight in the INT group (50%) reported a history of diabetes.

Table 2: Demographics

Variables	Control		Treatment	
	n	Mean ± SD	n	Mean ± SD
Gender	4	4 (100%) male	8	7 (87.5%) male
Age in years	4	59.00 ±9.9	8	61.5 ± 4.7

Oral Tests

With regard to clinical features of the sampled sites (Table 3), there were no significant differences within the CT group for all periodontal parameters at baseline and at four months ($p < 0.05$, signed rank test). Within the INT group, the results show that there were significant ($p < 0.05$, signed rank test) changes in Average PD (0.82mm reduction, p=0.0078), BOP (28% reduction, p=0.0078) and Average GI (0.78 reduction, p=0.0078) at four months compared to baseline (Figure 2). percentage of BOP than the control group (treatment: 28% average reduction, control: 2% average increase, p=0.0727).

Periodontal Parameters (Table 3)

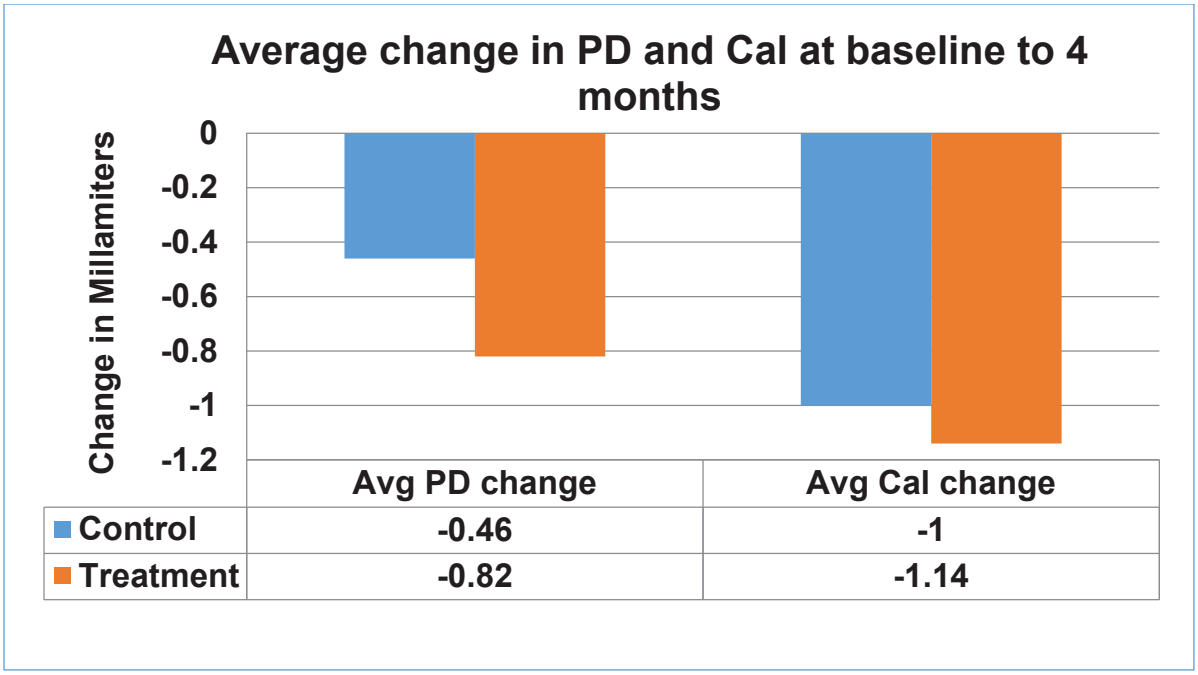

Figure 1: Graph of change in Pocket depth and Clinical Attachment Loss at baseline to four months in both the control and intensive intervention group. No significant change was noted between or among the two groups.

An exact Wilcoxon rank sum test for group comparison on the pre- and post-changes was also completed. The results show that the treatment group had significantly different Average GI change than the control group (treatment: 0.78 average reduction, control: 0.06 average reduction, p=0.0283) and marginally significantly different changes in percentage of BOP than the control group (treatment: 28% average reduction, control: 2% average increase, p=0.0727; Figure 2).

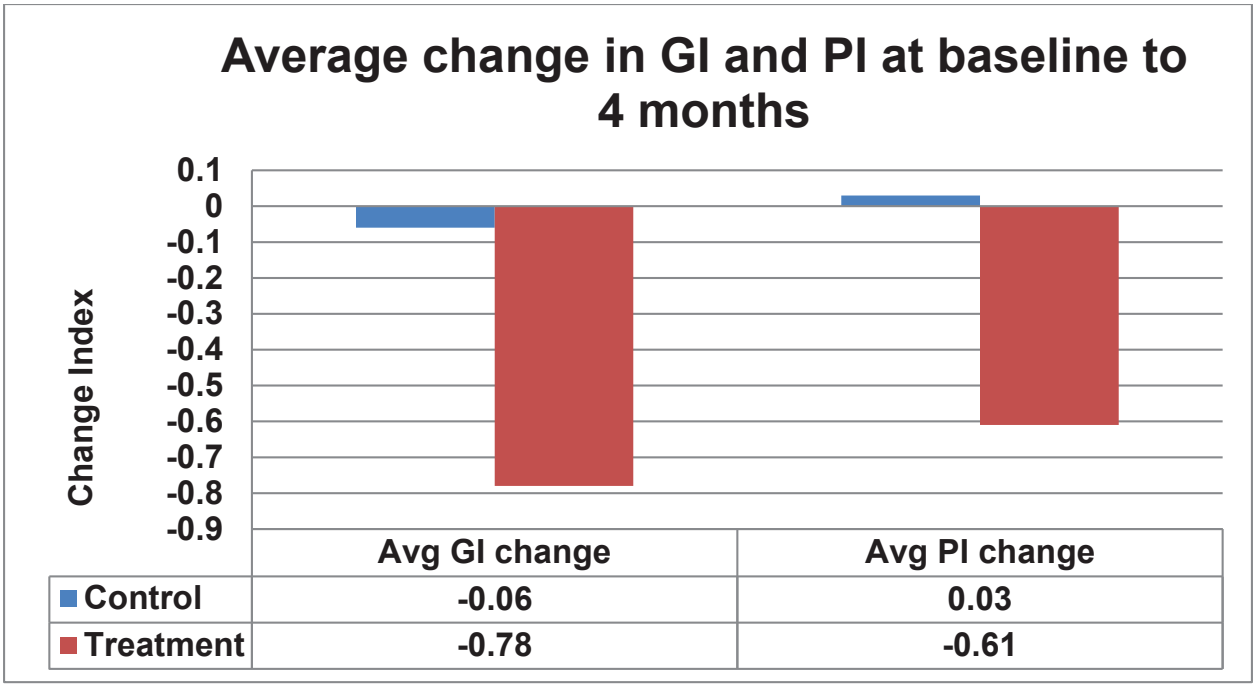

Figure 2: Graph of average change in Gingival and Plaque index from baseline to four months for both the control and intensive intervention group. Exact Wilcoxon rank sum test for group comparison noted that the treatment group had significantly different Average GI change than the control group but no significant difference was noted between groups in PI.

Table 3: Periodontal Parameters

Variables	Time	Community treatment group		Intensive intervention group		P value**
		n	Mean ± SD	n	Mean ± SD	
Average PD in Millimeters	Baseline 4 months Change P value*	4 4 4	3.55 ± 0.82 3.09 ± 0.57 -0.46 ± 0.30 0.1250	8 8 8	3.15 ± 0.51 2.34 ± 0.58 -0.82 ± 0.37 0.0078	0.1091
Average CAL	Baseline 4 months Change P value*	4 4 4	3.80 ± 1.56 2.80 ± 2.07 -1.00 ± 1.66 0.3750	8 8 8	3.33 ± 0.94 2.20 ± 1.25 -1.14 ± 1.16 0.0391	0.9333
% BOP	Baseline 4 months Change P value*	4 4 4	60 ± 31 62 ± 19 2 ± 27 1.0000	8 8 8	55 ± 14 27 ± 19 -28 ± 11 0.0078	0.0727

Average GI	Baseline 4 months Change P value*	4 4 4	1.62 ± 0.66 1.56 ± 0.87 -0.06 ± 0.41 1.0000	8 8 8	1.57 ± 0.49 0.80 ± 0.40 -0.78 ± 0.45 0.0078	0.0283
Average PI	Baseline 4 months Change P value*	4 4 4	1.10 ± 0.38 1.13 ± 0.58 0.03 ± 0.25 0.8750	8 8 8	1.49 ± 0.59 0.87 ± 0.50 -0.61 ± 0.97 0.1484	0.2141

*signed rank test for pre and post comparison within a group. The results show that there were significant changes in Average PD (0.82 reduction, p=0.0078)), BOP (28% reduction, p=0.0078) and Average GI (0.78 reduction, p=0.0078) at 4 months compared to baseline in treatment group.

** Exact Wilcoxon rank sum test for group comparison on the pre- and post- change. The results show that the treatment group had significantly different Average GI change than the control group (treatment: 0.78 average reduction, control: 0.06 average reduction, p=0.0283) and marginally significantly different BOP change than the control group (treatment: 28% average reduction, control: 2% average increase, p=0.0727).

The percentage change in BOP (Figure 3)…showed

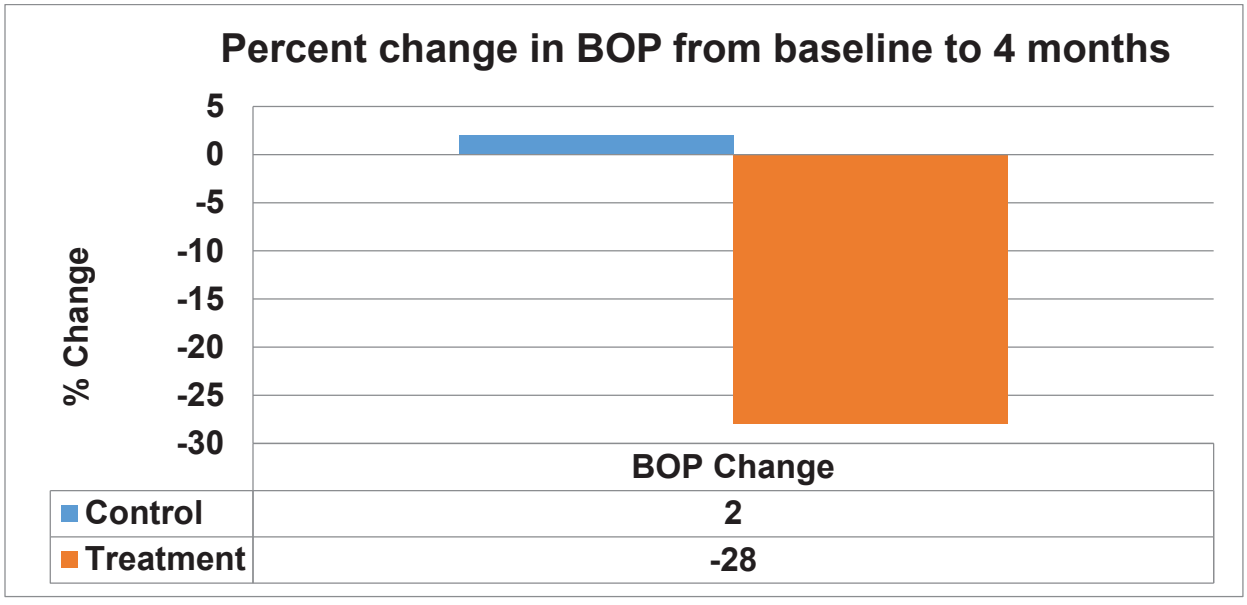

Figure 3: Graph of percent change in Bleeding on Probing from baseline to four months for both the control and intensive intervention group. A significantly different change in percent BOP was noted using Exact Wilcoxon rank sum test for group comparison on the pre- and post- change.

DISCUSSION

During the four-month course of the study, only one patient received dental treatment from an outside dental provider. This visit was the result of a recommendation from one of our UCSF residents to have a carious lesion filled. Additionally, none of the patients received any periodontal care outside of the care of our hygienist. Our results demonstrated significant improvement in the measured periodontal parameters after SC/RP and adjunctive antibiotic therapy (Arestin) in the INT group. Despite the presence of compromised renal function in patients with chronic periodontitis, non-surgical periodontal treatment significantly decreased the average pocket depth by 0.82 ± 0.37mms (P= 0.0078), improved the average clinical attachment level 1.14 ± 1.16 mms (P=0.0391), decreased bleeding on probing by an average of 28% ± 11% (P=0.0078), and improved the gingival index by an average of 0.78 ± 0.45 (P=0.0078). Aside from the general oral complications these patients faced, the results of this study are promising, as the general state of disability, depression of the immunologic response, and masking of signs and symptoms by drug therapy could be expected to have an impact on improving periodontal outcomes.[15] Contrary to the belief that patients with compromised renal function may not respond to periodontal treatment due to decreased immune function,[9] the patients in the INT group showed a significant improvement in bleeding on probing (P=0.0727) and average gingival index (0.0283) when compared to the CT group. Therefore, we can assume that the ill adapted immunity of patients with compromised renal function did not have a negative effect on the improvement of periodontal parameters such as BOP and GI.

Although our data did not show a significant change in PI between and within groups, it is important to note that there was a considerable change between the two groups. Evidence exists that demonstrates growth of dental plaque and inflammation of gingival tissue are ubiquitous and strongly linked to periodontitis irrespective of age, gender or racial/ethnic identification[1]. The impact of controlling the presence of plaque which results in inflammation is also associated with BOP and thus explains why a

significant change can be seen in BOP levels, GI, and Pocket Depth after plaque was decreased through non-surgical intervention.

Our data is in agreement with several studies that show an improvement in periodontal parameters in CKD patients with post non-surgical periodontal therapy. It is important to note that when comparing groups, the control group in all of the following studies completed non-surgical periodontal therapy on periodontally involved patients without CKD. This is in contrast to our study, in which the control group was periodontaly involved with CKD but did not obtain periodontal therapy. One can speculate that, although the control groups differ in modality of disease and treatment, our patients should be more likely to demonstrate an improvement from baseline when comparing between the two groups.

In a study by Artese *et al.,* (2010) [4], the authors compared clinical periodontal measurements and eGFR at baseline and at three months after non-surgical periodontal therapy. Periodontal treatment led to significant improvements in the periodontal parameters (visible plaque index, gingival bleeding index, suppuration, BOP, PD, and attachment loss) and eGFR in both patients with CKD and periodontal disease and in patients without CKD and periodontal disease. Artese did not find any significant difference in periodontal outcomes between groups. In a study by Vilela *et al.,* (2011)[17] the CKD cohort had a significant improvement in BOP, PD, CAL, GI, PI and in sites with PPD greater than 5-mm. Comparison between the control group and the patients with CKD found that there was a significant difference in CAL and PD greater than 5-mm. This is in contrast to our study, in which we did not see a marked improvement in CAL between the two groups. It is most likely that this discrepancy can be attributed to the low sample size of our population, as a significant improvement in CAL was observed within the intensive intervention group, itself. Similarly, Graziani *et al.,* (2010)[10] demonstrated a statistically significant improvement on post non-

surgical therapy between baseline and 90 days for the experimental population in periodontal outcome measures PD, CAL, the number and percentage of pockets greater than 5-mm.

One of the weaknesses of our study is the lack of proper control groups. It would have been a benefit to include treatment of periodontally-involved patients who were free of CKD. This extra arm of the study, though more costly, would have provided a reference to compare the magnitude of periodontal improvement between a cohort with healthy renal function and those with CKD. Multiple potential confounders and risk factors, which are common for both periodontal disease and CKD, were not considered in the statistical analysis of our study. It has been demonstrated that age, race/ethnicity, gender, income, education, poorly controlled diabetes, smoking, obesity, C-reactive protein level, cholesterol level, high-density lipoprotein cholesterol level, and low-density lipoprotein cholesterol level can possibly mediate the relationship between CKD and periodontal disease.[5, 9] These variables were not controlled for in the statistical analysis due to the lack of sample size or availability of information. However, it is noteworthy to mention that both groups contained a proportional amount of subjects with a history of diabetes.

CONCLUSION

Our results showed that the intensive intervention groups experienced a significant improvement in the majority of the periodontal parameters measured (PD, BOP, CAL, and GI). Additionally, BOP and GI were demonstrated to improve statistically when compared between groups. Moreover, it is important that we as health care providers understand the importance of interdisciplinary care and communication between the dentist and the physician in order to evaluate periodontal health, reinforce oral hygiene, and recommend proper treatment to those patients afflicted with CKD. Given the likelihood of the demonstrated potential benefits of non-surgical periodontal therapy, longitudinal studies should be completed to determine the

bidirectional relationship as well as to assess the role of inflammation and its link between CKD and periodontal disease.

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