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A Randomized Controlled Trial of Intensive Periodontal Therapy on Metabolic and Inflammatory Markers in Patients With ESRD: Results of an Exploratory Study

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Abstract

Background—Periodontitis is a novel risk factor for inflammation and cardiovascular disease in the dialysis population. Limited information about the impact of periodontal therapy in patients receiving dialysis exists.

Study Design—Randomized, controlled trial to assess feasibility and gather preliminary data.

Setting & Participants—Dialysis patients with moderate/severe chronic periodontitis.

Intervention—Intensive treatment, consisting of scaling and root planing, extraction of hopeless teeth, and placement of local delivery antibiotics was performed at the baseline visit for treatment group patients and following study completion for control group patients.

Outcomes—Outcomes were feasibility (screening, recruitment, enrollment, adverse events and study withdrawal/completion), clinical periodontal parameters [probing depth (PD), clinical attachment level, bleeding on probing, gingival index (GI), and plaque index] and serum albumin and interleukin 6 levels at 3 and 6 months postintervention.

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Trial registration: www.ClinicalTrials.gov; study number: NCT00937976.

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Results—A total of 342 dialysis patients were approached for participation: 53 were randomized, with 26 participants assigned to immediate treatment and 27 to a control arm for treatment after 6 months. 51 patients completed baseline appointments; 46 were available for 3 month follow up and 45 were available for 6 month follow up examinations. 43 participants completed all visits. At 3 months, there was a statistically significant improvement for the treatment group compared to the control group for 3 periodontal parameters: mean PD (p=0.008), extent PD ≥ 4 mm (p=0.02), and extent GI ≥1 (p=0.01). By 6 months, however, the difference between groups was no longer present for any variable except PD ≥ 4 mm (p=0.04). There was no significant difference between the groups for serum albumin or high-sensitivity interleukin 6 at any time point, when adjusted for body mass index, diabetic status, and plaque index.

Limitations—Small sample size and relatively healthy population. Imbalance in diabetes.

Conclusions—This small trial demonstrates successful cooperation between dentists and nephrologists and successful recruitment, treatment and retention of dialysis patients with periodontitis. Larger studies with longer follow up are needed to determine whether treatment can improve markers of inflammation and morbidity.

Keywords

kidney diseases; hemodialysis; end stage renal disease; periodontal diseases; periodontitis/complications

Systemic inflammation, common among patients receiving dialysis therapy, is a strong predictor of morbidity and mortality. Studies have demonstrated abnormal levels of serum inflammatory biomarkers in 30%–60% of all dialysis patients[1–4]. Such markers, including low serum albumin and high C-reactive protein (CRP), are associated with an increased risk of cardiovascular disease (CVD) and death[5, 6].

Periodontitis is a damaging inflammatory process of the dental support structures. Bacteria, present in oral biofilms at numbers greater than 10^{10} organisms [7], infiltrate the space created by periodontitis and elicit local inflammation [8, 9]. In susceptible individuals, organisms can evade local defenses and invade the circulation to induce a systemic inflammatory response, including the elevation of CRP and interleukin 6 (IL-6)[10–12]. The association between periodontal infection and risk for CVD and atherosclerosis are postulated to be mediated partly through a series of acute phase reactants and inflammatory cytokines[13–18].

Recent evidence has demonstrated a high burden of periodontitis among patients with chronic kidney disease[19–23]. Studies suggest that among patients receiving hemodialysis, the presence of severe periodontitis is associated with low levels of serum albumin [24, 25]. Furthermore, two independent cohorts of hemodialysis patients have demonstrated that severe periodontitis at baseline is associated with an increased risk of CVD-related death during the follow-up period compared to no disease[26, 27].

There is limited information on the effect of treatment for periodontitis in the dialysis population. Information from such studies could help to reduce periodontitis associated morbidity [26, 27]. As a first step, we conducted a small exploratory study to determine the feasibility of treating periodontitis among patients receiving dialysis therapy. Our goals were: (1) to determine the impact of treatment on clinical measures of periodontitis severity; (2) to determine the impact of periodontal treatment on pre-specified laboratory parameters (serum albumin and interleukin-6); and (3) to assess recruitment and retention of patients. We present the findings of a small, randomized, controlled study examining the effect of periodontal treatment among patients receiving outpatient dialysis.

Methods

Participants

Hemodialysis and peritoneal dialysis patients were recruited from clinics within a 25 mile radius of the University of North Carolina (UNC) from July 2008 through December 2009. Patients were approached at outpatient dialysis clinics by one of the study authors (MW). Interested patients were verbally screened, and consent for an intra-oral screening was obtained for those who met verbal criteria (criteria that did not require an intra-oral examination). All enrolled subjects met the following inclusion criteria: presence of moderate/severe periodontitis[28] (≥2 teeth with ≥ 6 mm clinical attachment loss and at least 1 site with probing depth > 5 mm), receiving dialysis for at least 3 months, English speaking, ability and willingness to give written informed consent, age 18–80 years, and presence of 12 or more teeth.

Subjects were excluded for the following reasons: severe co-morbid conditions likely to affect life expectancy within one year (for example, metastatic cancer); dementia; pregnancy or lactation; inability to take oral medications; allergy or intolerance to minocycline, tetracyclines or polyglycolate polymers; allergy to both penicillin and clindamycin; severe dental caries; pulpal or mucosal disease that would interfere with periodontal therapy; any condition that would, in the judgment of the clinician or patient's physician, be a contraindication to dental treatment; and inability or unwillingness to follow the study protocol. Written informed consent and HIPAA consent were obtained from all subjects. The study was approved by the Biomedical Institutional Review Board of the UNC and was conducted in accordance with the Helsinki Declaration of 1975, revised in 2000.

Subjects were randomized (1:1) to either treatment or control group using a randomized block design generated by the study statistician using SAS Proc Plan (www.sas.com) and were assigned sequentially by study staff (blinded, non-examiner). The treatment group received periodontal therapy following the baseline examination; the control group received periodontal therapy at the conclusion of the study. Subjects were given appointments for a baseline visit at the clinical research facility of the dental school in Chapel Hill, NC. Study appointments occurred on the subjects' inter-dialysis day with the exception of those receiving peritoneal dialysis.

Treatment protocol

Periodontal treatment consisted of removal of supra- and subgingival microbial deposits via scaling and root planing (SRP) under local anesthesia using hand and ultrasonic instruments. Adjunctive local delivery antimicrobial therapy with controlled-release microsphere-encapsulated, biodegradable minocycline was administered to all sites with >5 mm probing depths at the time of SRP and at the 3 and 6 month follow up appointments, thus the term "intensive therapy." Any teeth deemed hopeless[29] (gross decay, severe bone loss with severe mobility, abscess, etc.) were extracted at the time of scaling and root planing in the quadrant. Treatment was done in one or two appointments by one of three trained providers.

All subjects received verbal and written oral hygiene instruction at each visit. Each subject received instructions and demonstrations in the use of a soft-bristled toothbrush with the modified Bass technique (wherein a toothbrush is held at a 45-degree angle against teeth and gumline then used in circular fashion) and the use of floss with the "c-wrap" technique (wherein floss is wrapped around tooth in a "c" shape).

Treatment group subjects received follow up examinations at 3 and 6 months after completion of treatment; control group subjects received follow up examinations at 3 and 6 months after baseline and received treatment at the conclusion of the study.

Clinical Parameters

Examiners were calibrated for accuracy and repeatability against a gold standard. An initial calibration with all examiners was performed, followed by yearly re-calibrations. Percent agreement with the gold standard was >90% for probing depth (PD) and clinical attachment loss measurements (CAL), and Kappa scores were >0.90.

Subject medical histories were reviewed and updated at every appointment. The following were assessed on all subjects at baseline, 3 months and 6 months. *Plaque Index (PI):* The modified Silness and Löe plaque and stain index[30] was scored for three facial surfaces (distofacial, facial, mesiofacial) and the direct lingual surfaces of each tooth. *Gingival Index (GI):* The Löe and Silness gingival index[31] was scored on three facial surfaces (distofacial, facial, mesiofacial) and the direct lingual surfaces following a 1-mm subgingival sweep. *Probing Depth (PD)*: A manual periodontal probe (UNC-15; manufacturer name) was used to measure PD. PD was measured from the free gingival margin to the base of the pocket, and was recorded in whole millimeters (rounded down). *Clinical Attachment Level (CAL)*: CAL was calculated using the formula: probing depth measurement minus gingival margin to cemento-enamel junction (CEJ) measurement (where a gingival margin coronal to the CEJ is recorded as a positive number, rounded down to the nearest millimeter). *Bleeding on Probing (BOP)*: BOP was assessed and recorded after probing measurements and CAL for each quadrant. PD, CAL, BOP were recorded for six sites per tooth for all teeth present.

A 14-radiograph periapical series was obtained to assess additional pathology. Referrals for treatment were made as needed.

Serological Parameters

Venous blood (2 vials of 5–7 ml each) was collected under sterile technique. Blood was processed into serum within 2 hours after collection: whole blood was kept at room temperature for 30–45 minutes to allow a clot to form, and then centrifuged for 12 minutes at ≥ 1500 rcf to separate serum. Serum was aliquoted into barcode-labeled microfuge tubes, frozen at −80°C and stored until analysis. High-sensivity interleukin-6 was assayed by high-sensitivity enzyme-linked immunofluorescent assay (ELISA; R&D Systems, www.rndsystems.com) and read out using a SpectraMax M2 from Molecular Devices (www.moleculardevices.com). Serum albumin was analyzed via colorimetric assay on dry slides (Ortho Johnson and Johnson, www.orthoclinical.com).

Statistics

A sample size of 25 per treatment group at 6 months follow-up was calculated to provide 80% power to detect statistically significant differences in the mean levels of the primary outcomes between the two treatments that are as small as 79% of the applicable standard deviation, using two-sided 0.05 significance tests. The estimated standard deviation of serum albumin is 0.53, and the minimum detectable difference is 0.42. These power calculations were based upon a simple two-group comparison of a single outcome variable at the six month follow-up visit with the independent t-test.

Additional variables considered included age (years), gender (male or female), body mass index (BMI in kg/m^2), diabetic status (diabetic or not), dialysis type (hemodialysis or peritoneal dialysis), time on dialysis (months), smoking status (current smoker or non-smoker), and a personal medical history of heart disease (known history or no known history).

Statistical analysis was performed using SAS (SAS 9.1.3, SAS Institute Inc www.sas.com). Exploratory univariate data analyses using plots (horizontal bar charts, box plots, and

normal probability plots) and test statistics were conducted to examine distributions of periodontitis parameters, co-morbid variables (listed earlier), and outcome variables and to inspect for outliers and missing data. Outliers (more than two standard deviations from the mean) were detected and checked for accuracy. Analysis with outliers excluded did not significantly alter conclusions for any outcome parameter. Analysis included means and standard deviation for continuous variables and percents for categorical variables. Skewed variables were analyzed using median and interquartile ranges; comparisons were made based on the Wilcoxon rank-sum test. Baseline comparisons between treatment groups for other variables were done using chi-squared tests and t-tests, as appropriate.

A general linear model (GLM) with correlated errors [32] was fit to the baseline and with three and six month follow-up data for each outcome. An unstructured covariance matrix for within-subject errors was specified using the repeated statement of SAS Proc MIXED. As covariates, the model included dummy variables for time (3 months and 6 months with baseline as the reference), treatment group, and the interaction of time and treatment group. Model-based estimates of the mean levels of outcomes at each time were produced. The Kenward-Roger degrees-of-freedom adjustment was used to test the (null) hypotheses of no treatment differences in mean changes of the outcome relative to baseline at three and six months, respectively. P-values <0.05 were considered statistically significant.

Results

A total of 342 dialysis patients were approached for participation (Figure 1). Of these, 262 patients (77%) agreed to be screened (Figure 2). Interested subjects were verbally screened and consent for an intra-oral screening was obtained for those who met verbal criteria. The most common reasons for exclusion were: presence of less than 12 teeth in the mouth (n=97 [37%]); and age >80 years (n=26 [10%]). Interestingly, only 13 of those screened (5%) were excluded by probing depth (i.e. they did not have sufficient periodontal disease to qualify). Other reasons cited for non-participation included “fear of dentists” and “lack of time.” Of those screened, 68 patients (26%) met all inclusion criteria and agreed to participate. Fifteen subjects (22%) of those who initially agreed to participate did not attend the baseline examination. Fifty-three subjects (15% of approached patients) were enrolled and randomized. Twenty-six subjects were randomized to the periodontal treatment group and 27 subjects were randomized to the control group. Two subjects were randomized, but withdrew prior to baseline and were excluded from analysis. Full clinical parameters and serum samples were obtained for 51 subjects at baseline, for 46 subjects at 3 months and for 45 subjects at 6 months. Forty-three subjects completed all study visits. Two subjects (both in treatment group) missed 3 month follow up only and were not withdrawn. Three subjects (1 in control group: medical instability; 2 in treatment group: received kidney transplants) missed the 6 month follow up only and were withdrawn from the study. Three subjects (all in control group: 1 no-show/lost to follow up, 1 deceased, 1 medical instability) missed both the 3 and 6 month follow up and were withdrawn from the study. Twenty-eight total adverse events (13, control group; 15, treatment group) were reported among twenty-three subjects. Twenty-four events were deemed unrelated (for example: subject diagnosed with hypothyroidism). Two mild events were probably related (dentinal sensitivity). Two events were possibly related (increase in probing depth, catheter infection). Ten unrelated events were classified as severe.

Mean participant age was 53.4 +/− 9.79 (standard deviation [SD]; range, 30–75) years. Statistically, treatment and control groups did not differ significantly at baseline by any variable measured (Table 1); however, about half (51%) were diabetic, and the diabetics were unevenly distributed between control and treatment groups with 62% of diabetics randomized to the treatment group and 38% randomized to the control group (p=0.07).

Based on BMI-based definitions,[33] Eleven percent of subjects were normal weight (BMI, 18.50–24.99 kg/m^2), 47% were overweight (BMI, 25.00–29.99 kg/m^2) and 42% were obese (BMI, ≥30.00 kg/m^2). Median time on dialysis was 19 (overall range, 3–176) months. Only 14% were current cigarette smokers. Eighty-five percent were on hemodialysis (versus peritoneal dialysis). The most common cause of kidney failure was hypertension, followed by diabetes.

At baseline, the overall mean number of teeth per subject was 23 +/− 5, mean extent (% of sites) with bleeding on probing was 44% +/− 23% and mean extent plaque score ≥1 was 90% +/− 19%. On average, extent of sites with clinical attachment loss ≥3 was 41% +/− 26%. Seventy five percent had 4 or more sites with ≥5mm probing depth. Mean baseline serum albumin was 4.13g/dl (standard error [SE], 0.10) for the control group and 4.40g/dl (SE, 0.10) for the treatment group. Mean high-sensitivity IL-6 was 6.40 pg/ml (SE, 2.35) for the control group and 8.60 (SE, 2.44) for the treatment group. There were no statistically significant differences between clinical periodontal parameters or serum markers at baseline.

Figure 3 summarizes the clinical periodontal parameters for control versus treatment group at baseline, 3 months and 6 months. At 3 months, there was a statistically significant improvement for the treatment group compared to the control group for three periodontal parameters (Table 2): mean PD (p=0.008), extent PD ≥4mm (p=0.02), and extent GI ≥1 (p=0.01). There were apparent improvements in two parameters, mean CAL and extent CAL ≥3mm, in the treatment group compared with the control group, but the differences were nonsignificant (p=0.08 and 0.09, respectively). By 6 months, however, the difference between groups was no longer present for any variable except extent PD≥4mm (p=0.04). Adjusting for BMI, diabetic status, and plaque index did not significantly alter results and these variables were not included in the final model.

General linear models with correlated errors for repeated measures were used for comparisons of serum parameters between treatment groups. There was no difference between the groups for serum albumin or high-sensitivity IL-6 at any time point, when adjusted for BMI, diabetic status, and plaque index (Table 3). No subjects improved from a serum albumin of <4g/dl to >4g/dl during the course of the study.

Discussion

We successfully completed a randomized controlled study to determine the efficacy of intensive periodontal treatment in patients with end-stage renal disease. Intensive treatment statistically significantly improved several measures of periodontal health at 3 months; however at 6 months only extent PD ≥4mm improvement remained statistically significant. Intensive treatment was not associated with an improvement in high-sensitivity IL-6 or serum albumin levels at either 3 or 6 months of follow-up. Interestingly, control subjects also exhibited some improvement in clinical parameters, potentially attributable to oral hygiene instruction and their awareness of being observed [34] which may decrease the observed impact of periodontal therapy.

Limited information about the effect of periodontal therapy on patients receiving renal dialysis exists. Previous studies in non-dialysis populations have demonstrated that treatment of periodontitis improves flow-mediated dilation, a marker of endothelial function and intermediate measure of cardiovascular disease[35–37]. In fact, a recent randomized, controlled trial showed a remarkable improvement of 2% in flow-mediated dilation for 6 months after scaling and root planing[38]. Another recent paper[39] demonstrated that treatment of periodontal disease improved CRP values in the dialysis population. Given these intervention studies showing benefit, and the preponderance of epidemiological evidence in

the chronic kidney disease population[24, 26, 27], we were surprised by the modest beneficial effect. Potential explanations of our findings center around four inter-related issues: the relative healthiness of the participants, a greater proportion of diabetics in the treatment arm, lack of maintenance therapy, and insufficient power.

Patients enrolled into the study were relatively healthy compared to most individuals receiving dialysis therapy [40] and to patients in previous observational studies[24–27]. In fact, several variables speak to the relative health of this population, including elevated serum albumin[41–44], elevated BMI[45–48], and the ability of the patients to attend appointments on non-dialysis days. Previous observational studies have been non-invasive and examinations were performed on-site in less than 20 minutes. They did not require additional time or travel commitment by the participants. In the present study, participants were required to attend five 1–2 hour appointments at the dental clinic. In this study population, this requirement likely selected for healthier patients with the time and ability to attend appointments. The pre-specified requirement of a set number of teeth (12) may have excluded patients with the most severe periodontitis since fewer teeth may reflect tooth loss due to extensive disease. Previous epidemiologic studies demonstrating the association of periodontal disease with low albumin [24, 25] and mortality [26, 27] had less stringent restrictions for minimum number of teeth.

Despite randomization, 62% of diabetics were assigned to the treatment group while only 38% of diabetics were assigned to the control group. Diabetes and periodontitis have a complex interrelationship, each affecting the other [49]. Diabetes is often referred to as one of the most important systemic disease risk factors for periodontitis. Reduced wound healing ability has a profound impact on periodontitis expression as well as on response to periodontal therapy. This may have dampened observed treatment effects.

Treatment, consisting of one-time scaling and root planing and administration of local delivery minocycline, may not have been sufficient. The treatment group displayed statistically significant improvement or an apparent trend for improvement in 5 of the 7 clinical parameters at the 3 month follow up appointment followed by partial relapse in every parameter at 6 months. While slightly improved, compliance with oral hygiene instruction in all groups was generally poor, as demonstrated by high plaque scores. Even following treatment, plaque levels in the treatment group at 3 and 6 months remained higher (PI range, 86.0%–93%) than is generally considered compatible with health (PI range, 10%–15%). These findings emphasize the need for regular periodontal maintenance, particularly given poor oral hygiene among these subjects and their inability to maintain clinical improvements over time with home care alone.

Studies have demonstrated the critical role of regular maintenance in controlling periodontitis [50,51]. Maintenance typically consists of plaque and calculus removal, assessment of periodontal and oral health status and oral hygiene evaluation/instruction performed on an individualized interval (commonly every three months). Improvements in periodontal health can often be maintained using this approach despite a patient's own poor oral hygiene[52]. Maintenance was not provided in this study, as the goal of this study was to examine the effect of a single round of scaling and root planing. Given the poor home care among this population as indicated by high levels of plaque and BOP, subjects would likely have benefitted from a maintenance program.

Initial power calculations were based on 25 subjects per group, however, by 6 months, only 23 subjects remained in the treatment group and 22 remained in the control group. *Post hoc* analysis of our data shows that in our sample, the power of detecting a 0.15 observed difference in serum albumin is 0.14. Thus, this study did not have adequate power to detect

differences between the groups in serum albumin; the results of this study serve as preliminary and feasibility data and provide insight into future study design. Based on our observations, using the three month high-sensivity IL-6 data and given delta scores for control and treatment of 0.213 +/− 9.018 and −1.887 +/−9.018, respectively, power at 0.8 results in a necessary sample size of 582 subjects for a full scale trial. Using the six month IL-6 data and given delta scores of 0.524 +/− 11.033 and −3.186 +/− 11.033, respectively, power at 0.8 results in a necessary sample size of 280 subjects for a full scale trial.

Given the modest observed effects, we caution against concluding that treatment of periodontitis may be ineffective. Rather, the findings of this study serve to inform the design of future trials in this field. Limitations in this trial include small sample size and uneven distribution of diabetics between the study groups. For future trials, a longer follow up time may be needed to observe impacts on inflammatory markers. Additionally, given results from other studies, a broader range of inflammatory markers may present a more complete profile. With respect to inclusion criteria, restrictions on age range and number of teeth should be broadened to include participants with age greater than 80 years and with fewer teeth. Periodontal treatment should be expanded to include maintenance visits every 3 months or less. Given the large number of patients screened for participation, a study with multiple centers would be preferable to a single center attempt.

In summary, this small trial demonstrates successful cooperation between dentists and nephrologists and successful recruitment, treatment and retention of dialysis patients with periodontitis. Treatment of periodontitis in dialysis patients improved clinical measures of periodontitis severity but did not produce an observable impact on serum markers of inflammation. Larger studies are needed to examine the effect of treatment on biomarkers and clinically significant events such as cardiovascular disease morbidity and mortality.

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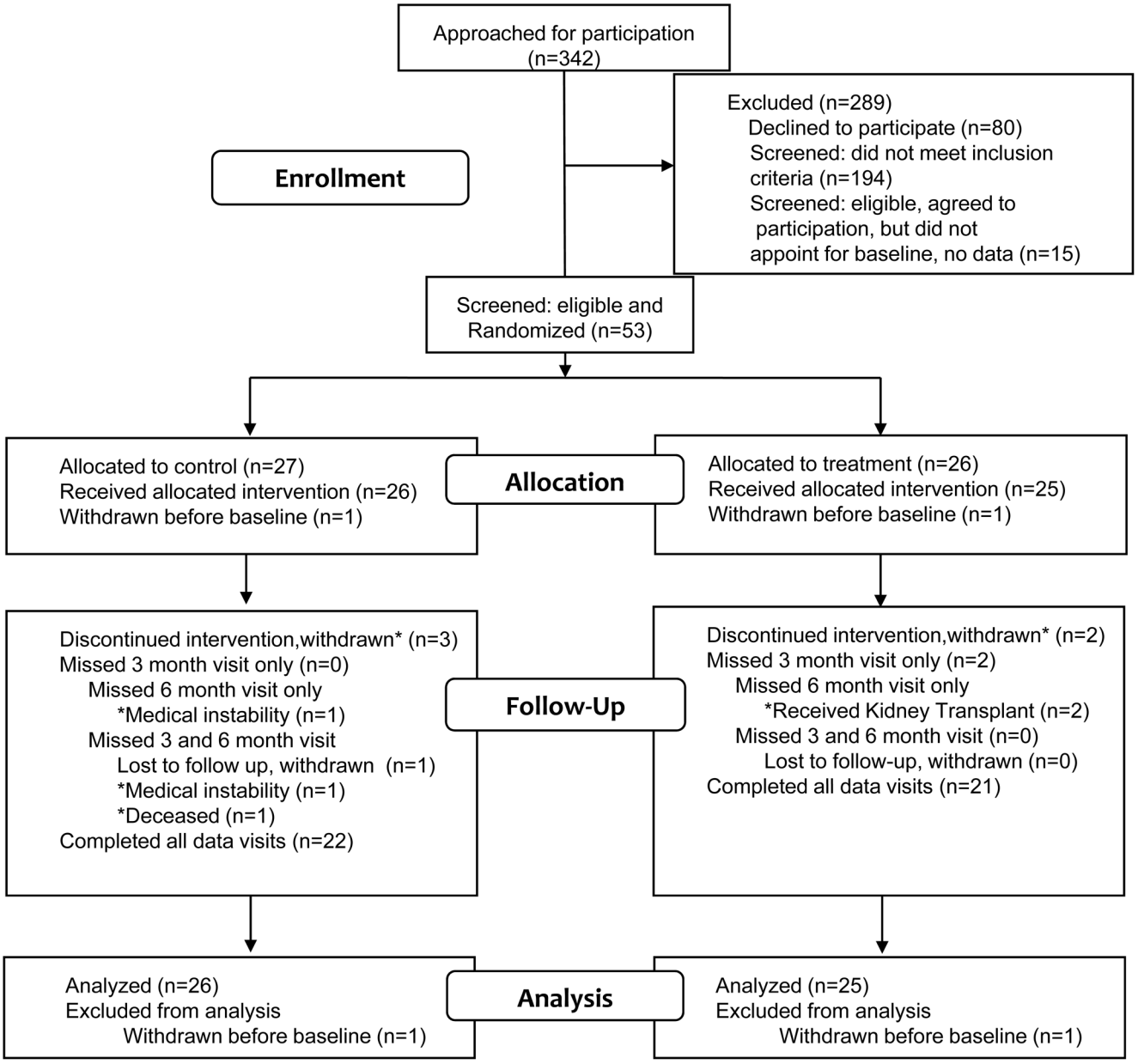

Figure 1.
CONSORT[53] Study Flow Diagram

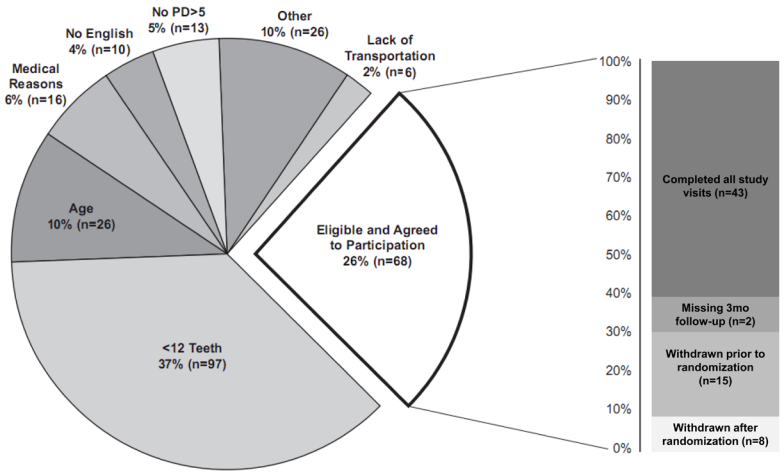

Figure 2.
Status of Screened Subjects and Reasons for Ineligibility (n=262). PD, probing depth.

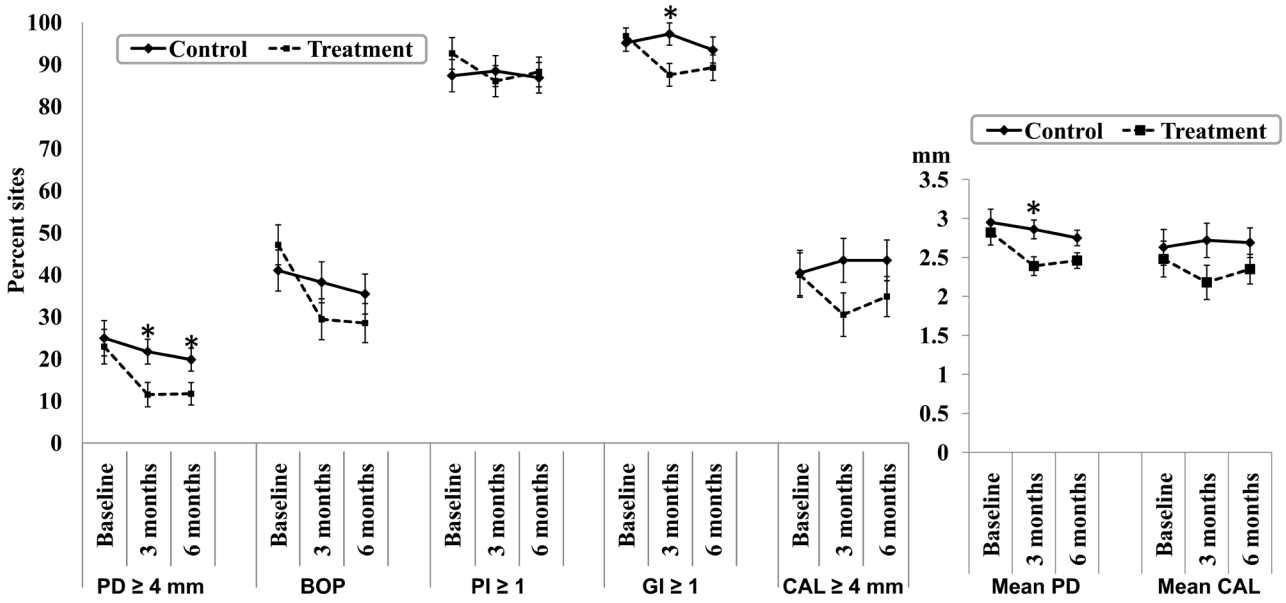

Figure 3.

Mean (SE) Clinical Measures for Each Time Point by Treatment Group(PD= probing depth, BOP= bleeding on probing, PI= plaque index, GI= gingival index, CAL= clinical attachment level) *significant at p≤0.05

Table 1

Baseline characteristics of control and treatment groups

Characteristic	Control Group (n=26)	Treatment Group (n=25)	p-values*
Sex			0.5
Male	18 (69%)	15 (60%)	
Female	8 (31%)	10 (40%)	
Race			0.6
African-American	23 (88%)	21 (84%)	
Non-African	3 (12%)	4 (16%)	
American			
Smoker			0.9
Never	14 (54%)	15 (60%)	
Former	8 (31%)	7 (28%)	
Current	4 (15%)	3 (12%)	
Heart Disease			0.6
No	17 (65%)	18 (72%)	
Yes	9 (35%)	7 (28%)	
Diabetes			0.07
No	16 (62%)	9 (36%)	
Yes	10 (38%)	16 (64%)	
Age (y)	52.7 (10.6)	54.1 (9.0)	0.6
BMI (kg/m2)	31.9 (6.4)	31.4 (8.3)	0.8
Dialysis Vintage ** **(mo)**	18 (8–89)	22 (10–65)	0.9
Dialysis type			0.6
Hemodialysis	23 (88%)	21 (84%)	
Peritoneal	3 (12%)	4 (16%)	

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables as mean +/− standard deviation or median (interquartile range).

* Significance tests for comparisons between treatment and control group based on 2-sample t-test for continuous patient characteristics and Pearson's chi-square test for categorical patient characteristics. None were statistically significant at $p<0.05$.

** Dialysis vintage is a skewed variable; hence median (interquartile ranges) is reported. P-value is based on the Wilcoxon rank-sum test.

BMI, body mass index

Table 2

Clinical Measures for Each Time Point by Treatment Group

Clinical Measures	Group	Baseline*,**	3 mo**	6 mo**	*P*	
					Baseline-3 mo	Baseline-6 mo
Mean probing depth	Control	3.0 (0.17)	2.9 (0.12)	2.8 (0.10)	**0.008**	0.06
	Treatment	2.8 (0.16)	2.4 (0.12)	2.5 (0.10)		
Extent probing depth ≥4mm	Control	24.9 (4.21)	21.7 (2.93)	19.8 (2.74)	**0.02**	**0.04**
	Treatment	22.9 (4.11)	11.5 (2.91)	11.7 (2.68)		
Extent bleeding on probing	Control	41.0 (4.87)	38.2 (4.87)	35.4 (4.76)	0.2	0.3
	Treatment	47.1 (4.76)	29.4 (4.87)	28.5 (4.66)		
Extent gingival index ≥1	Control	95.1 (1.99)	97.2 (2.65)	93.4 (3.10)	**0.01**	0.3
	Treatment	96.7 (1.95)	87.5 (2.70)	89.2 (3.03)		
Extent plaque index ≥1	Control	87.3 (3.84)	88.4 (3.68)	86.8 (3.63)	0.7	0.8
	Treatment	92.6 (3.76)	86.0 (3.70)	88.2 (3.54)		
Mean clinical attachment level	Control	2.6 (0.23)	2.7 (0.22)	2.7 (0.19)	0.08	0.2
	Treatment	2.5 (0.23)	2.2 (0.22)	2.4 (0.19)		
Extent clinical attachment level ≥3mm	Control	40.4 (5.38)	43.4 (5.23)	43.4 (4.85)	0.09	0.2
	Treatment	39.9 (5.27)	30.5 (5.16)	34.8 (4.75)		

Note: Values are presented as mean (standard error).

*No significant differences were found between groups at baseline.

**General linear models with correlated errors

Table 3

Serum Markers for Each Time Point by Treatment Group

Serum markers	Group	Baseline*,**	3 mo**	6 mo**	P	
					Baseline-3 mo	Baseline-6 mo
Albumin (g/dl)	Control	4.13 (0.10)	3.99 (0.10)	3.93 (0.11)	0.2	0.4
	Treatment	4.40 (0.10)	4.24 (0.10)	4.16 (0.10)		
hsIL-6(pg/ml)	Control	6.40 (2.35)	6.52 (1.24)	7.03 (1.26)	0.8	0.9
	Treatment	8.60 (2.44)	7.04 (1.28)	7.05 (1.28)		

Note: Values are given as mean (standard error)

*No significant differences were found between groups at baseline

**General linear models with correlated errors, adjusted for body mass index, diabetic status, and plaque index, with each control variable set at its own respective mean.

hsIL-6, high-sensitivity interleukin 6.