IRB Review
IRB NUMBER: 16-111-1
IRB APPROVAL DATE: 06/07/2018

Title:
Novel **PA**radigm to improve **I**nflammatory burden in ES**R**D (rePAIR): A pilot and feasibility Randomized Controlled Trial

May 7, 2018

Sponsor: Effie Ioannidou
UConn Health
263 Farmington Avenue
Farmington, CT 06030

Principal Investigator: Effie Ioannidou
Director, Dental Clinical Research Center
UConn Health
263 Farmington Avenue
Farmington, CT 06030

Phone: (860) 679-2367

Fax: (860) 679-1027

IRB Review
IRB NUMBER: 16-111-1
IRB APPROVAL DATE: 06/07/2018

TABLE OF CONTENTS

IRB Review
IRB NUMBER: 16-111-1
IRB APPROVAL DATE: 06/07/2018

1. Title: Novel **PA**radigm to improve **I**nflammatory burden in ES**R**D (rePAIR): A pilot and feasibility Randomized Controlled Trial

IRB Review
IRB NUMBER: 16-111-1
IRB APPROVAL DATE: 06/07/2018

2. Background

Why is the project being proposed?: Given the importance of inflammation as a predictor of cardiovascular mortality in ESRD[21, 24], reductions in biochemical inflammatory markers have been proposed as critical target outcomes in this population[25]. Several anti-inflammatory strategies have been utilized in this direction assessing nutritional[26] as well as pharmacological interventions[23, 27, 28]. Although the results of these trials hold promise, many investigators recognized different sources of inflammation in these patients, which need to be resolved in order to achieve the most optimal responses[21, 29]. As expected, the inflammatory modulation requires concurrent therapy of the multiple comorbidities, which characterize this population[30, 31 32]. The present multidisciplinary proposal is significant because it promises to:

1. Reduce inflammatory burden in ESRD through systematic and ongoing oral health and behavioral interventions treating oral infections within dialysis units.
2. Improve access to care and quality of life in ESRD as measured by validated surveys and biomarkers.
3. Facilitate care quality improvement and management of ESRD patients as well as expand performance of dialysis units.

This proposal focuses on targeting chronic periodontitis, a chronic inflammatory disease of biofilm etiology, which causes connective tissue and bone destruction and, consequently, leads to tooth loss[1 33]. Chronic periodontitis is associated with increased risk for atherosclerosis, adverse pregnancy outcomes, rheumatoid arthritis, chronic obstructive pulmonary disease and aspiration pneumonia[34, 35 36-38]. Although recent epidemiological evidence showed a severe periodontitis prevalence of ~8.5% in the general US population[2], this prevalence increased up to ~40% in some racial groups with CKD[3, 4, 9 5]. The PI has extensively worked on oral health in CKD within the scope of her NIH/NIDCR K23 Mentored Patient-Oriented Research Career Development Award (K23DE018689), which has successfully achieved 4 major goals: 1) to assess the prevalence of periodontal infections in CKD, 2) to examine the impact of periodontitis on the systemic inflammatory status of CKD patients following oral interventions and 3) to produce pilot data on inflammation and oxidative stress and 4) to develop multidisciplinary partnerships securing strong recruitment strategies and effective regulatory processes.

Using the National Health and Nutrition Examination Survey (NHANES) III database, we demonstrated significantly higher periodontitis prevalence accentuated by racial disparities in CKD (Table 1)[5], which exceeds 50% in ESRD[6, 39-42]. Despite periodontitis recognition as a critical public health problem (Healthy People 2020), disease awareness in CKD/ESRD populations is low[43]. Therefore, oral health promotion as well as effective treatment and prevention with focus on improving systemic inflammation and oxidative stress should become a priority in these populations.

	Non-Hispanic Whites			Non-Hispanic Blacks			Mexican-Americans		
	CKD N = 437	Non-CKD N = 4216	*p*-Value	CKD N = 88	Non-CKD N = 3182	*p*-Value	CKD N = 81	Non-CKD N = 3600	*p*-Value
Periodontitis	12.9 (1.8)[2]	7.5 (0.4)	0.001	38.9 (5.8)	14.6 (0.5)	0.001	37.3 (6.8)	9.0 (0.5)	0.001

Table 1: Periodontitis prevalence as stratified by race in CKD and non-CKD population (n=11,604). Data represents Prevalence (%) and standard deviation (SD). Notice the statistically significant difference in prevalence between CKD and non-CKD populations in every racial group. For the entire sample, inflation-adjusted prevalence was 35.28% in CKD (data not shown) (Ioannidou & Swede, 2011)

Why is the research needed?

Within the last decades, the high inflammatory burden in ESRD has been attributed to the "uremic puzzle" with pieces developing and connecting in an intricate manner[20] contributing to cardiovascular (CVD) mortality. We now know that the complexity of the "uremic puzzle" extents past the Framingham CVD risk factors involving systemic inflammation and oxidative stress as variables strongly associated with poor CVD outcomes in CKD[20]. Overwhelming evidence has indicated that the enzymatic activity of myeloperoxidase links oxidative stress and inflammation in uremia emphasizing the importance of both in the atherosclerotic process[22]. Consequently, research has focused on identifying factors contributing to systemic inflammation and oxidative stress at different levels. At an ethnic level, several culture-related dietary habits have been identified as anti-inflammatory correlating with low CVD risk[26]. Dialysis related factors such as membrane bio-incompatibility, type of access, impure dialysate have also been linked to systemic inflammation[53]. At the patient level, additional comorbid factors including bacterial infections, volume overload, failed transplant and depression have been implicated in the elevation of serum CRP [32] and were targeted in anti-inflammatory therapeutic efforts[21, 32].

Variables	Crude	Model 1	Model 2	Model 3	Model 4
OR (CI 95%)					
Periodontitis: Yes	1.60 (1.11-2.31)	1.53 (1.04-2.25)	1.34 (0.89-2.02)	1.19 (0.77-1.82)	1.18 (0.81-1.73)
Extent of Periodontitis ≥ 30% sites	1.64 (1.11-2.43)	1.60 (1.04-2.49)	1.86 (1.04-3.34)	2.01 (1.19-3.61)	2.03 (1.21-3.66)

Crude model—unadjusted; Model 1—age, sex and race; Model 2—age, sex, race, diabetic control and duration, BMI, smoking, antihyperlipidemic medication, antibiotic and antiviral medication, CVD history, education, and income; Model 3 (full model)—all previous variables plus CKD stages; and Model 4—parsimonious model.

Table 2: Logistic regression models confirming the impact of periodontitis extent and severity on inflammation in CKD

In the same context, the American Heart Association has recognized the independent association between periodontitis and systemic inflammation[54] as expressed by high levels of inflammatory biomarkers such as interleukin 6 (IL-6) and C-reactive protein (CRP)[55-57]. Our group and others produced evidence supporting the contribution of periodontitis to inflammation in CKD as measured by hsCRP levels[7, 9, 11]. As seen in Table 2 chronic periodontitis is associated with ~100% increase in the odds of elevated serum CRP levels in the parsimonious regression model. Moreover, the impact of periodontitis on serum CRP levels has been shown to be significant in ESRD with a dose-response association between hsCRP and periodontitis stages [58].

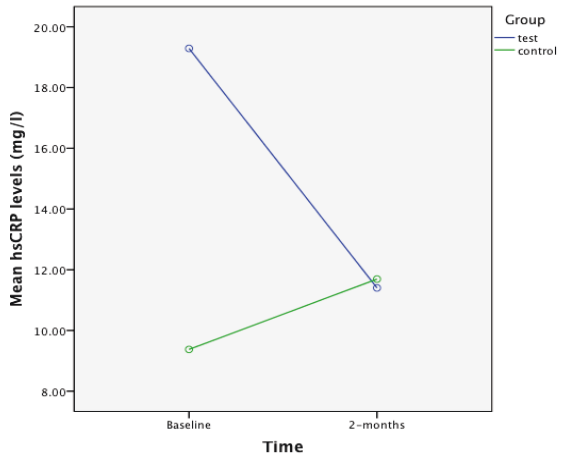

Figure 2: Serum hsCRP is shown to decrease in the intervention arm as opposed to the control within the 2-month period (p=0.13)

As confirmed by analogy[59], other infections have shown to result in increased levels of inflammatory mediators in dialysis patients and to consequently contribute to atherosclerosis process and increased mortality [18, 48, 60]. Therefore, the relationship between periodontitis and CKD is potentially bi-directional in nature, with CKD/ESRD not only potentiating periodontitis incidence, but periodontitis likely contributing to sustained inflammation and poor outcomes in CKD/ESRD. These observations led to interventional studies with a goal to assess the effect of oral periodontal therapy on inflammatory mediators as surrogate markers of CVD risk. Within the scope of the K award, we conducted a pilot clinical trial working closely with our collaborator at the University of Washington, Dr. Himmelfarb, and studying the effect of periodontal therapy on systemic inflammation and oxidative stress in ESRD patients with periodontitis (NCT 01094639). We recruited 16 dialysis patients, who were randomly assigned to two arms. One arm received a single course of periodontal therapy and the other arm was untreated during the observation period. For both arms oral examination and blood

draw were performed at baseline and at the 2-month follow-up. The recruitment took place with the following inclusion criteria: a) older than 21 years, b) having periodontitis [61], c) non-smoker, d) no vascular access infection within the last month, e) no periodontal therapy within the last year. We quantified serum hsCRP (inflammation) and F2-isofurans (oxidative stress) as primary outcomes. Using general linear modeling, we found that hsCRP (Fig. 2) and F2-isofurans (Fig.3) were reduced following periodontal therapy as compared to the control group (Ioannidou & Himmelfarb, unpublished data), although no statistically significant difference was observed due to the limited sample size. More specifically, the 40% reduction in hsCRP levels was found to be similar to the hsCRP reduction observed following conversion from the central venous catheter to fistula[18]. These results are in agreement with other reports confirming a short-term (2-month follow-up) positive treatment effect on the inflammatory markers in ESRD[15, 16, 62-66]. However, only one long-term randomized controlled trial on periodontal treatment effect extended to 6-months in ESRD and revealed no difference in inflammatory changes between the arms[15]. In a critical appraisal of the above trial, the main study limitation was the episodic, single periodontal therapy approach without any attempt for maintenance, as confirmed by the poor oral hygiene scores. Clearly, that approach was not effective enough to **promote** optimal oral hygiene, and **prevent** recurrent periodontitis and **control** systemic inflammation [67-69]. In our model, the dialysis outpatient centers could serve as an archetype for continuous in center oral health maintenance as shown below in our approach and recruitment strategy. For anti-inflammatory strategies to be effective, they inclusively need to consider all comorbidities[30, 31]. Consequently, the scientific question in this proposal is: could systematic and repeated periodontal interventions modulate systemic inflammation in ESRD?

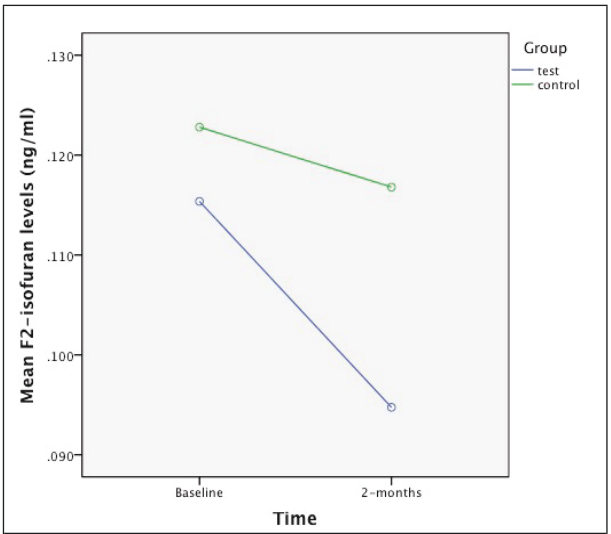

Figure 3: Plasma F2-isofuran levels are shown to decrease dramatically in the intervention arm from baseline to 2-month as compared to the control arm (p=0.2)

Innovation: The highly prevalent periodontal infection, although recognized as a cause of persistent inflammation in ESRD[6] and associated with increased CVD mortality risk[8, 58], its treatment and prevention in a constant and systematic manner has never been studied. Currently, only 11% of CKD/ESRD individuals have one dental visit a year[43] due to low socioeconomic status and low oral health awareness. Therefore, well-designed interventional studies are essential for the development of systematic treatment and maintenance protocols in ESRD. As kidney transplant is considered highly preferred modality of renal replacement, infection-free oral environment is a major priority, relevant to the approximately 19% of dialysis patients receiving a kidney transplant within the first year of dialysis[70]. The proposed study is innovative because it is the first study to:

- Assess the long-term effect of repeated oral health interventions on serial changes of systemic inflammatory and oxidative stress as well as nutritional biomarkers in ESRD patients.
- Offer a global testing of our hypothesis by focusing on patient-reported outcomes as supported by US Department of Health and Human Services, Food and Drug Administration guidelines on clinical studies (FDA guidelines, 2009) and the NIH roadmap for re-engineering the Clinical Research Enterprise (2002).
- Establish treatment protocol safety data by documenting adverse events within the observation period.
- Implement a systematic oral care model not in an academic center but in the urban setting of the selected dialysis units, embracing population ethnic and socioeconomic diversity.

This pioneer proposal will directly address oral preventive practices leading to an infection free environment and improving ESRD outcomes. If the feasibility of this model is established, then larger clinical trials may be developed to solidify the knowledge on effective approaches and guidelines targeting persistent inflammation in ESRD.

3. Hypotheses, aims and objectives

Hypothesis:

Given the well-documented inflammatory and oxidative stress burden in ESRD and its implication to cardiovascular (CVD) mortality [19], current research focuses on anti-inflammatory nutritional and pharmacological strategies [20-23]. Although results from these trials hold promise, different sources of inflammation such as untreated periodontitis have been recognized in ESRD limiting the magnitude of the effect[21]. Therefore, untreated periodontitis may be a forgotten comorbidity. This proposal aims to assess the anti-inflammatory effect of repeated and regular oral health interventions, which will target periodontitis in ESRD. **We hypothesize** that there is a difference in the response to repeated and ongoing vs. single periodontal interventions as measured by: a) patient-centered outcomes, b) inflammatory, oxidative stress and nutritional biomarkers as well as c) clinical oral outcomes. This will be achieved by following specific aims:

Specific aim 1: We aim to compare the difference (Δ) in patient-centered as well as clinical oral outcomes between ESRD subjects receiving repeated (Test group) and the standard-of-care (Control) periodontal therapy. *For this aim, we will measure and compare patient-centered outcome (Oral Health Impact Profile-14 survey) reflecting patient's perspective on oral health at baseline and 6-months. The clinical oral outcomes will evaluate the clinical response and effectiveness of the intervention at each time point.*

Specific aim 2: *We aim to compare the difference* (Δ) in *outcomes of systemic inflammation (C-reactive protein, Interleukin 6), oxidative stress (F2-isoprostanes, and isofurans), and nutrition (albumin) in the repeated vs. standard-of-care periodontal therapy in ESRD at baseline and 6-months. To accomplish this, we will collect blood samples from all patients at each time point. Serial changes of the inflammatory and oxidative stress markers will also be evaluated during the observational period and correlated with clinical disease markers.*

The PI has extensively worked on the ESRD/CKD-periodontitis interactions and has developed strong partnerships with several outpatient dialysis units in two states, which will facilitate patient recruitment. With this study, we will change the paradigm of care in ESRD proposing a novel model of oral interventions. We aim to show that, as with any other therapeutic approaches, repeated (not episodic) oral interventions could be more effective in promoting oral health and controlling systemic inflammation in ESRD. This pioneer proposal will directly address oral preventive practices leading to an infection free oral environment and improving ESRD outcomes. If the feasibility of this model is established, then longitudinal studies will aim to determine the synergistic systematic treatment effect of multiple comorbidities including periodontitis on all cause and CVD mortality.

4. Study Design & Procedures

- Screening Procedures and who will perform them: ESRD subjects will be screened at visit 1 by a licensed dentist or Registered Dental Hygienist.

Recruitment Strategy: As a result of the K23 award, the PI has developed a strong multidisciplinary research team that successfully partnered with several dialysis outpatient units in Connecticut and Massachusetts. This resulted in a community-based network among the Principal Investigator, the study coordinator, calibrated dental providers, nephrologists, nurses, and dieticians in the units. Moreover, we have developed a recruitment strategy involving an active and close collaboration with the unit stakeholders (nephrologist, nurse manager and dietician) in order to achieve higher study acceptance rates [71]. Physical limitations and fatigue, which may prevent this population from independent everyday transportation, have been identified as major barriers for research study participation in this

population[72]. Hence, to overcome these obstacles, we have developed a community-based model, which has been effective with the retention and adherence rates. Based on this model, we will utilize mobile dental units, which facilitate examinations and periodontal therapy in the dialysis units using the isolation rooms to secure privacy and confidentiality. We systematically review our recruitment and retention rates as well as feedback from patients in the team's monthly meetings.

ESRD patients will be recruited at the Dialysis Units of the University of Connecticut Health Center, and the DCI Unit in Manchester, CT. The recruitment strategy includes study fliers posted in different locations including UCONN Health Nephrology and Dental Clinics and Dialysis Outpatient Units as well as DCI Unit in Manchester, CT. The PI has included Dr. Trivedi (UCONN Health and DCI Units) as a Co-Investigator in the study. All recruitment strategies and material will be approved by UCONN Institutional Review Board (IRB). Once UCONN Health IRB is approved, while DCI will follow a separate IRB process utilizing UCONN IRB approved consent forms.

Patient selection will be based upon administrative patient list review and/or study flyer. In case administrative list review is employed, medical record review will be performed by the dialysis unit director in each unit with the utilization of our screening form. The nephrologist/dialysis unit director will then review the proposed selection list based on clinical judgment and the pre-screening criteria. We have also developed recruitment tools (Pre-screening Form, study brochures), which are practical and easy to implement in order to assist the nephrologist and dialysis personnel during the pre-screening process. Once the pre-screening process is completed, the ESRD subjects will contact the study coordinator for screening appointment. After an explanation of the study, the overall risk/benefits analysis, written consent will be sought from each of the participants. Following consent, patients will receive a brief oral exam to establish eligibility based on the Screening Form. Dental sessions will be scheduled based on patient choice but preferably prior dialysis session to minimize patient fatigue.

Our team has an extensive experience with the dental management of ESRD patients. Our protocol has derived from a close collaboration between the dental and renal teams.

- Prior to entering the study and any oral intervention, ESRD patient with recent complete blood count is cleared by the nephrologist.
- Prior and during the dental procedures, vital signs are monitored as a standard of care in dialysis.
- Since several drug metabolism and elimination takes place in the kidney, and for protocol adhesion, only analgesics such as acetaminophen and anti-inflammatory drugs such as aspirin will be prescribed and "realistically dosed", resulting to either a dose reduction or prolongation of the dosing interval. If any other anti-inflammatory medication is needed, the patient will be excluded from the study (as per exclusion criteria)
- There is no evidence-based recommendation on the use of prophylactic antibiotics in the dental management of ESRD patients due to the lack of data on the duration and effects of transient bacteremia post dental intervention. Our preliminary study, which was conducted without antibiotics, had in no adverse events to report. Transient bacteremia has been shown to resolve in less than 20min in systemically healthy individuals (Lockhart et al., 2008). Antibiotic overutilization and misuse result in selection of resistant microorganisms and reduced antibiotic efficacy. Therefore, in our study we plan to use antibiotics wisely only if recommended by the primary nephrologist for high-risk patients.

Methods

Study design and Subject selection: The proposed study will be a two parallel arm feasibility clinical trial that will recruit 72 ESRD subjects with periodontitis in a model of computerized block randomization, which will facilitate recruitment in each outpatient dialysis unit. Blocks will be determined as per 2x2x2 a priori categorization of age, race and gender. More specifically, the participants in 2 dialysis units (UCONN Dialysis/ DCI and DCI Manchester) will be randomly assigned to the study arms using a computer randomization program. As a result, once sequences are determined by the statistician, they will be concealed in opaque envelops and opened prior to the first recruitment in the unit. This study will include participants treated with dialysis 3 times a week. Out of 900 ESRD patients in recruitment sites, we estimated approximately 450 patients with periodontitis. Individuals will be included in the

IRB Review
IRB NUMBER: 16-111-1
IRB APPROVAL DATE: 06/07/2018

study if they are older than 21 years old; if they are ESRD on dialysis; if they have chronic periodontitis as defined before [61]; if life expectancy is more than 1 year; if they have can provide consent form. Individuals will be excluded from the study if they had periodontal treatment within a year prior to the study initiation; if they have AIDS, or active malignancy; if they poorly adhere to dialysis protocol; in anticipation for kidney transplant during study period; if they are pregnant; if they have dementia; if they take anti-inflammatory medication, except aspirin≤325mg/d; if they use temporary catheter for dialysis access.

Population: This trial will recruit ESRD adult patients with periodontitis fulfilling the eligibility criteria below.

Inclusion criteria: Individuals will be included in the study if they are older than 21 years old; if they are ESRD on dialysis; if they have a minimum of 12 teeth; if they have chronic periodontitis as defined by the presence of at least two sites with CAL≥4mm or at least two sites with PD≥5mm not on the same tooth[26]; if they have no history of periodontal treatment within a year; if life expectancy is more than one year; or if they have can provide consent form.

Exclusion criteria: Individuals will be excluded from the study if they had periodontal treatment within a year prior to the study initiation; if they have HIV/AIDS, or active malignancy; if they poorly adhere to dialysis treatment; in anticipation for kidney transplant during study period; if they are pregnant; if they have dementia; if they take anti-inflammatory medication, except aspirin≤325mg/d; or if they use temporary catheter for dialysis access.

- Subject characteristics and justifications:
  - Age: **21 years of age or older**
  - Ethnicity: **Please see NIH enrollment data in the grant application**
  - Gender: **Same as above**
  - Vulnerable Population NA
  - Other characteristics - (e.g. vulnerable populations; primary language etc.): NA

Intervention: The Test arm will receive treatment and maintenance sessions. Briefly, treatment sessions will include oral hygiene behavioral modification and scaling and root planning (removing the bacterial biofilm and calculus below the gum line) in order to eliminate etiologic factors and control periodontal inflammation. More specifically, the behavioral interventions will include oral hygiene instructions with specific techniques of tooth brushing and flossing demonstrated on typodont. In order to standardize the oral hygiene session (intervention fidelity), the providers will be trained to follow specific oral hygiene guidelines with re-calibration on the protocol procedures every 3 months to maintain study quality control. Once the treatment sessions are completed, the patients will enter the maintenance phase and will be followed for 6 months. In this phase, the patients will receive systematic supportive periodontal treatment (tooth cleanings above the gum line with re-enforcement of oral hygiene). Outcomes will be assessed at 2-, 4-, and 6-months.

Control: The Control arm will receive only a single session of treatment without maintenance sessions (see visit Table in *Human Subject Protection* section). Outcomes will be assessed at 2-, 4-, and 6-months.

Dental Treatment Needs: Throughout the course of the study, additional dental needs for both Arms (Test and Control) will be addressed with immediate referral to the Advanced General Dentistry Program at the UCONN Health or the subject's own general dentist.

Strategies to Improve Adherence: We systematically review our recruitment and retention rates as well as feedback from patients in the team's bi-weekly meetings. For treatment fidelity, the study staff will be trained to follow an oral hygiene script and guidelines followed by re-calibration on the protocol procedures every three months to maintain study quality control. The OHIP-14 will be filled during oral hygiene session in an interactive interview form following provider training on the questionnaire administration to control for treatment fidelity.

Outcomes and Rationale:

1) Inflammatory Markers (Primary Outcomes) and Oxidative Stress Markers (Secondary outcomes): We aim to measure serum CRP (primary outcome) as a biomarker of inflammation as well as IL-6, F2 isofurans and F2 isoprostanes as markers of oxidative stress linked to atherosclerosis and poor CVD in ESRD[22]. A single serum CRP elevated measure has been shown to predict poor outcomes and sudden death in ESRD[75]. Additional studies showed that IL-6 has been determined as a direct promoter of atherosclerosis and protein energy wasting through mechanisms of vascular calcification, muscle catabolism and cell aging [32] predicting poor outcomes in ESRD[75]. In addition to testing the primary and secondary outcomes at baseline and 6-month, we will compare serial changes of the biomarkers throughout the study period at 2- and 4-month time points. Moreover, we will also measure F2 isoprostanes and isofurans, which are chemically stable, precise and easily detectable markers of lipid peroxidation[76] associated with poor outcomes in ESRD.[20]

2) Patient-centered outcome (Secondary outcome): Given the wide recognition of patient-centered outcome research by the Agency for Healthcare Research and Quality (AHRQ) and the NIH [77], the validated OHIP-14 (true outcome) will evaluate patient's perception of oral status change [78] and predictably assess periodontal treatment effect on oral health quality of life [79, 80]. Oral health perception has been determined fair to poor in groups of ESRD patients [81]. The oral health related quality of life will be assessed with the OHIP-14 questionnaire [82]. The response codes for the items in this tool are based on a five-point scale, ranging from "never" to "all the time".

3) Clinical Periodontal Parameters (Secondary Outcomes): The baseline full mouth periodontal examination will include missing teeth, probing depth (PD), bleeding on probing (BOP), clinical attachment loss (CAL), and plaque score (PS) at six sites on all teeth. BOP is an indicator of gingival (gum) inflammation and presence of active disease [83]. Periodontal parameters will be measured at baseline, at 2-, 4- and 6-months. Changes in probing depth (ΔPD) and BOP (ΔBOP) will be considered as the clinical outcome of treatment effectiveness and clinical response.

4) Nutrition Biomarkers: Serum albumin levels have been widely associated with malnutrition and mortality in ESRD [84]. We will use albumin levels less than 3.6g/dL as cutoff for malnutrition [85, 86]. As serum albumin has been associated with poor oral health status (Ioannidou et a. 2013), we will assess changes in these biomarkers as a result oral intervention.

5) Adverse Event Frequency (Secondary outcome): For this outcome, pain, swelling, number of analgesics used (continuous) and presence of oral ulcers (dichotomous) will be recorded. More specifically, pain and swelling will be measured by ordinal scale (10cm horizontal Visual Analogue Scale, VAS).

Study Procedures and who will perform them:

Pre-screen Phase:

The nephrologist will review the potential subject's medical record to determine patient eligibility based on the criteria of the Nephrologist Pre-screen Form questions. The nephrologist will present the study to the potential subject and provide DCRC study contact information. If the potential subject is interested in participating, they will call the DCRC. At the time of the phone call from the pre-screened potential subject, the DCRC study staff will read the telephone script and collect name and scheduled dialysis treatment dates and times in order to schedule visit 1.

Visit 1: ESRD subjects will be consented in the dialysis outpatient units. Following the consent, the medical history will be reviewed and vital signs will be tested. During the screening process, brief periodontal examination will be performed to clear the periodontal inclusion criteria.

Visit 2 (Baseline): Full mouth periodontal examination will include: numbers of missing teeth, pocket depth (PD), clinical attachment level (CAL), plaque score (PS), bleeding on probing (BOP). In the same visit the OHIP-14 will be contacted in an interactive form to the both arms. Blood sample (6.5ml) will be collected for baseline inflammatory, oxidative stress and nutritional markers for both arms.

Visits 3-4 (Day 0): Full mouth scaling/root planning (Deep cleaning below the gum line) under local anesthesia will be performed to remove etiologic factors of the disease in both arms in one or 2 appointments. At the end of the visit, both groups will receive oral hygiene instructions.

**After Visits 3-4 test and control arm visits numbers change.*

Test arm: *(see time table Test arm, pg.14)*

Visit 5; Test (1-month post-Day 0): Oral hygiene reinforcement and behavioral modification only for the Test arm.
Visit 6; Test (2-month post-Day 0): Full mouth periodontal examination including oral hygiene assessment will be performed. Both arms will receive the OHIP-14. Blood samples (6.5ml) will be collected for inflammatory, oxidative stress and nutritional markers for both arms. Only in the test arm, the subject will receive supportive periodontal treatment including supragingival debridement and mechanical instrumentation (tooth cleaning) and oral hygiene reinforcement. Any remaining pockets will be treated with limited deep cleaning with local anesthesia. The control arm will receive no intervention.
Visit 7; Test (3-month post-Day 0): Oral hygiene reinforcement and behavioral modification only for the Test arm.
Visit 8; Test (4-month interval post-Day 0): Full mouth periodontal examination including oral hygiene assessment will be performed. Both arms will receive the OHIP-14. Blood samples (6.5ml) will be collected for inflammatory, oxidative stress and nutritional markers for both arms. Only in the test arm, the subject will receive supportive periodontal treatment including supragingival debridement and mechanical instrumentation (tooth cleaning) and oral hygiene reinforcement. Any remaining pockets will be treated with limited deep cleaning with local anesthesia. The control arm will receive no intervention.
Visit 9; Test (5-month post-Day 0): Oral hygiene reinforcement and behavioral modification only for the Test arm.
Visit 10; Test (6-month post-Day 0): Full mouth periodontal examination including oral hygiene assessment will be performed. Both arms will receive the OHIP-14. Blood samples (6.5ml) will be collected for inflammatory, oxidative stress and nutritional markers for both arms. At the end of the study both arms will receive supportive periodontal treatment including supragingival debridement and mechanical instrumentation (tooth cleaning) and oral hygiene reinforcement. Any remaining pockets will be treated with limited deep cleaning with local anesthesia.

Control arm: *(see time table control arm, pg. 15)*
Visit 5; Control (2-month post-Day 0): Full mouth periodontal examination including oral hygiene assessment will be performed. Both arms will receive the OHIP-14. Blood samples (6.5ml) will be collected for inflammatory, oxidative stress and nutritional markers for both arms.
Visit 6; Control (4-month interval post-Day 0): Full mouth periodontal examination including oral hygiene assessment will be performed. Both arms will receive the OHIP-14. Blood samples (6.5ml) will be collected for inflammatory, oxidative stress and nutritional markers for both arms.
Visit 7; Control (6-month post-Day 0): Full mouth periodontal examination including oral hygiene assessment will be performed. Both arms will receive the OHIP-14. Blood samples (6.5ml) will be collected for inflammatory, oxidative stress and nutritional markers for both arms. At the end of the study both arms will receive supportive periodontal treatment including supragingival debridement and mechanical instrumentation (tooth cleaning) and oral hygiene reinforcement. Any remaining pockets will be treated with limited deep cleaning with local anesthesia.

Power Analysis*:* For power analysis, we assumed a Type I error rate α=0.05 and a Type II error, β =0.20 (1-β=0.80)[36]. Based on the preliminary data analysis of independent CRP changes, and after adjusting for time effect, we accepted a medium effect size (d = 0.67). Hence, within the pilot grant limitations, we calculated a sample size of 28 per arm. Given a reported 30% attrition rate in ESRD research, we aim to enroll up to 36 per arm. More importantly, pilot data from this trial will enable calculation of appropriate effect estimate and power analysis of a future large trial.
Therefore the sample size targets 72 enrolled participants with a ceiling of 90.

- Explain on what basis it is reasonable to assume that the sample size will be obtained: The PI has an established collaboration with several dialysis units in CT and MA. Therefore, we have an available pool of 900 ESRD subjects to be screened for a recruitment goal of 72. This is a very realist and predictable recruitment.

Recruitment and Consent Procedures: Patient recruitment was initiated on November 7th, 2017 with expected enrollment completion in April 2019. The trial is currently recruiting patients at UCONN Dialysis/DCI and DCI Manchester. The recruitment strategy includes study fliers posted in different locations including UCONN Health Nephrology, Dental Clinics and Dialysis Outpatient Units. All recruitment strategies and material were approved by UCONN Institutional Review Board (IRB) and DCI ARO. Figure 2 represents study flow chart.

The initial patient selection is based upon administrative and medical record review by the nurse manager with the utilization of the study's pre-screening form. The nephrologist reviews the patient selection and, based on clinical judgment and the pre-screening criteria makes the recommendation. We have also developed recruitment tools (pre-screening forms, study brochures), which are practical and easy to implement in order to assist the nephrologist and dialysis personnel during the pre-screening process. Once the pre-screening process is completed and the patient agrees to be approached, the study coordinator meets with the ESRD patient to present the study, the overall risk/benefits analysis, written consent is sought from each of the participants. The consent process may be extended to more than one meeting given the patient's level of fatigue [37].

Randomization and Allocation: The study follows a block randomization scheme. Blocks will be determined as per 2X2X2 a priori categorization of age, race and gender. More specifically, the participants in two dialysis units (UCONN Dialysis/DCI and DCI Manchester) will be randomly assigned to the study arms using a computer randomization program supervised by the study's biostatistician. Once sequences are determined, they remained concealed in opaque envelopes and opened prior to enrollment in the unit by the study coordinator.

Examiner calibration: The calibrated dental hygienist practices under the supervision of the Principle Investigator (PI). Following the calibration process, there was an agreement within ±1mm of 96%.

Blinding: At 6-month visit, the final assessment will be conducted by the PI, who will be blinded to the study arm.

Methods of Data Collection and Types of Data to be collected (may refer to attached surveys/ forms etc.)

Medical data collection: Once enrollment is completed, demographic, anthropometric, medical history data will be collected using a standardized data extraction form at baseline. The biochemical data will include serum albumin, dialysis adequacy (Kt/V), vitamin D levels. Potential confounders will include race, history and duration of diabetes, diabetic control, smoking history, history of CVD, body mass index (BMI), history of peripheral arterial disease and comorbid conditions. Additionally, in order to assess the magnitude of comorbidities, we will use the Charlson Comorbidity Score, which has been validated in ESRD and found appropriate to assess comorbidity prognostic impact[74]. Biochemical data will be examined at every study time point to assess medical changes.

Periodontal Data: Full mouth periodontal examination will include: numbers of missing teeth, pocket depth (PD), clinical attachment level (CAL), plaque score (PS), bleeding on probing (BOP). PS (O'Leary) is a dichotomous measure with the use of disclosing solution at six sites of all teeth. Pocket depth (PD) is the distance from the gingival margin to the base of the pocket is measured in mm. Bleeding on Probing (BOP) is scored after probing depth measurements are taken. Clinical attachment level (CAL) represents the distance from the cemento-enamel junction to the base of the pocket in mm. For all measures, six sites around each tooth will be examined: mesial-buccal, buccal, distal-buccal, distal-lingual, lingual and mesial-lingual.

Blood Collection and Analyses: Blood samples will be drawn prior to dialysis session at each participating dialysis unit. Samples will be centrifuged at 3000rpm for 15 minutes and then transported on ice. Samples will be coded and stored at -70°C. IL-6 and hsCRP levels will analyzed in dublicate by ELISA with kits from BioSource International (Carmillo, CA) and Diagnostic Systems Laboratories (Webster, TX). Oxidative stress markers will be quantified by simultaneous measurements of F2-isoprostane and isofuran concentrations with gas chromatography as described before [23]. Serum albumin will be measured by enhanced chemiluminescence immunoassay on Roche Modular Analyzer (Roche Diagnostics, Indianapolis, IN).

Statistical methods: All analyses will follow the intent-to-treat principle. Given an attrition of rate of approximately 30% in the dialysis population, missing data will likely be from different sources (e. g., failure to complete questionnaire, study dropout, death). We will, therefore, utilize the multiple imputation algorithms of the IBM SPSS Missing Values 22 software[39, 40] to impute missing data. Data will be screened as recommended[41]. Standard diagnostic procedures will examine whether multivariate outliers exist, as well test for deviations from normality and linearity among dependent measures. When continuous measures are skewed, linear transformation will be attempted in order to preserve the inherent power of the continuous metric[42]. Descriptive analysis for all four time points will be including continuous measures with means, medians and standard deviations. Given OHIP-14 responses are ordinal, we will calculate the responses based on the "simple count", score frequencies as used before[43] and analyzed with non-parametric methods. Spearman correlation analysis will be used to test associations between clinical parameters and patient's oral health perception. In order to assess the effect of the confounding factors on oral response, univariate model will correlate PD and CAL changes with the baseline parameters, demographic, socioeconomic status variables, as well as diabetic control, dialysis adequacy and vintage, vitamin D levels.

Exploratory univariate analysis and test statistics will be conducted to examine variable distribution. Outliers defined as more than two standard deviations from the mean will be detected. All biomarker variables will be tested for normality and logarithmically transformed if not normal. All analyses will include means and standard deviations for continuous variables and percentages for categorical variables. For skewed variables, analyses will show median and interquartile ranges. CRP and IL-6 changes (ΔCRP and ΔIL6) will be the dependent variables for hypothesis testing between the two arms. We will use a 3-level (time, subject, and cluster) hierarchical linear modeling technique[44] in the analysis of the data. The intercept (as a more robust indicator of initial baseline status) and slope (as an indicator for change, modeled as linear) are created for each subject. Predictors of inflammatory response will be assessed at subject level as well as subject nested within arm/recruitment site level. Additional secondary analyses will assess changes in the nutritional markers. The HLM will isolate predictors of inflammatory and oxidative stress response based on clinical phenotype, medical confounders, and cluster data.

Retention efforts: Physical limitations and fatigue, which may prevent this population from independent everyday transportation, have been identified as major reasons for research study participation in this population [38]. Hence, to overcome these difficulties, we have developed a community-based model, which has been effective with the retention and adherence rates. Based on this model, we will utilize a mobile dental unit that facilitates examinations and periodontal therapy in the isolation room of each hemodialysis unit. The isolation room secures privacy for both patient and provider. We systematically review our recruitment and retention rates as well as feedback from patients in the team's monthly meetings.

DATA AND SAFETY MONITORING PLAN

We have a Data and Safety Monitoring Plan in place, which will be submitted and approved by the IRB. Based on this plan, the data will be reviewed annually. Given that the clinical protocol procedures in the proposed study are standard of care procedures with minimal/slight increase over minimal risk, the individuals performing the safety monitoring will be the PI, the study coordinator, an institutional colleague, who is not involved in the study, and the IRB.

The data used for safety monitoring will be data related to:

1. Serious adverse events,
2. Dropout rates and reasons for the dropouts,
3. Enrollment numbers,
4. Analysis of outcome data and its relationship to potential changes in study design,
5. Protocol deviations
6. Un-blinded data

During the course of the study, a copy/summary of the monitor reports and/or minutes will be submitted to the IRB, Clinical Research Center (CRC) and NIH. The PI will evaluate the adverse events and determine whether the adverse events affect the risk/benefit ratio of the study and if modifications in the protocol and/or consent form are needed. In case of adverse events, the PI will report them to IRB, CRC, and NIH.

Protection of Confidentiality: The study will be conducted under the supervision of the PI, the co-Investigators and the collaborators. Best medical practices will followed during all procedures. All dialysis units are staffed with qualified and licensed personnel prepared to address emergencies. Further, nephrologist/attending is present at the dialysis units to clear the patient's medical status. During the course of the study, a copy/summary of the monitor reports and/or minutes will be submitted to the IRB, Clinical Research Center (CRC) and NIH. The PI will evaluate the adverse events and determine whether the adverse events affect the risk/benefit ratio of the study and if modifications in the protocol and/or consent form are needed. In case of adverse events, the PI will report them to IRB, CRC, and NIH. Study data will be maintained in a separate research record. All materials and data will be coded with number combinations. The code linking the study data to identifiers will be in the PI's computer protected by password. All study records will be coded in a locked cabinet in a secure area accessible only to research staff. A copy of the consent will be placed in the dialysis unit medical record. All electronic records (e.g. database, spreadsheets) will be password protected. Any computer hosting such files will have password protection to prevent access by unauthorized users. Access to study data will be restricted to the PI and Co-Is as well as the study key personnel. Data that will be shared with others will be coded to confidentiality protection.

Study Management: At the study initiation meeting, a delegation of responsibilities was carried out according to which, each investigator, and study personnel agreed to their assigned roles. The study PI has been in charge of the execution of this plan. Roles were assigned as justified in the research grant proposal. At the end of the initiation meeting, a study flow sheet was developed with all study procedures and practices. The flow sheet follows the study clinical schema as presented above. The flow sheet guarantees that all study activities are completed in the specific time points as described in the research strategy and the endpoints and outcomes are reached.

The study coordinator has been in charge of the regulatory management of the study, which includes the development of the regulatory binder with all essential documents. The regulatory binder includes study protocol, the study personnel human subject training log, the delegation of responsibilities form, the pre-screening and screening forms, consent forms, HIPAA forms, serious adverse events list, protocol deviation reports, and IRB approvals. The study subject chart contains all information about each study visit dated appropriately and precisely as well as a note declaring the procedures completed per visit. The pre-screening form is part of the chart. De-identified subjects that fail pre-screening are also maintained in a separate file. The study coordinator maintains a master subject log list, where all visits of all subjects are securely listed. This list guarantees accurate scheduling based on study time points.

The PI and the study coordinator are in charge for reporting the adverse events and also the follow up visit with the subject. Further, any protocol deviation is documented and reported. All laboratory assessments are maintained in a log list with specimen numbers and dates. An important part of the study is the quality management plan, which ensures study quality and adherence to the protocol standards. To achieve this, we have established an extensive monitoring plan to secure the study design, and achieve the endpoints and outcomes. Weekly study team communication and meetings are scheduled to prevent any misunderstandings or protocol gaps. The meetings help the team resolve problems and move to corrective actions at once before they become an established pattern. Every three months, the study subject charts are audited internally. To ensure the presence of consent form, pre-screen and screening form, lab requests, data collection forms, missed appointments and notes. Further, the electronic data files and all data variables are crosschecked with the source original data. The subject ID will be also crosschecked. Missing data will be left blank. Merging files of laboratory and clinical variables will be performed carefully based on ID variable.

Study Rigor and Transparency: The proposed trial follows a rigorous and transparent study design as requiring by the NIH capturing elements of trail design, pre-specified eligibility criteria, pre-specified primary and secondary outcomes, detailed intervention description to allow replication, intervention random allocation and concealment, blinding in outcome assessment, appropriate sample size calculations, explanation of interim analysis, as per CONSORT Guidelines[45, 46]. The proposed methods secures a robust and unbiased analysis as expected in a randomized controlled trial (RCT) and will ensure reproducibility of the experimental design[47]. With these efforts, we acknowledge the importance of research transparency through updated trial status, result and data reporting on Clinicaltrials.gov, as expected[48].

Timetable: Test Arm

Intervention	***Visit 1***	***Visit 2*** ***Baseline***	***Visit 3-4*** ***Day 0***	***Visit 5*** ***1-month***	***Visit 6*** ***2-month***	***Visit 7*** ***3-month***	***Visit 8*** ***4-month***	***Visit 9*** ***5-month***	***Visit 10*** ***6-month***
Consent Form	***x***								
Medical History Review/Vitals	***x***								
Periodontal Screening	***x***								
Full mouth periodontal exam		***x***			***x***		***x***		***x***
OHIP-14		***x***			***x***		***x***		***x***
Periodontal Therapy *(Deep periodontal cleaning)*			***x***						
Oral hygiene/ Behavioral modification			***x***	***x***	***x***	***x***	***x***	***x***	***x***
Maintenance *(Tooth Cleaning)*					***x***		***x***		***x***
Inflammatory Markers (CRP, IL-6)		***x***			***x***		***x***		***x***
Oxidative stress (F2 isoprostanes, isofurans)		***x***			***x***		***x***		***x***
Nutritional Markers (Albumin)		***x***			***x***		***x***		***x***

Control Arm (The shaded columns symbolize absence of study activities)

Intervention	***Visit 1***	***Visit 2*** ***Baseline***	***Visit 3-4*** ***Day 0***	***1-month***	***Visit 5*** ***2-month***	***3-month***	***Visit 6*** ***4-month***	***5-month***	***Visit 7*** ***6-month***
Consent Form	***x***								
Medical History	***x***								

IRB Review
IRB NUMBER: 16-111-1
IRB APPROVAL DATE: 06/07/2018

Review/Vitals									
Periodontal Screening	***x***								
Full mouth periodontal exam		***x***			***x***		***x***		***x***
OHIP-14		***x***			***x***		***x***		***x***
Periodontal Therapy *(Deep periodontal cleaning)*			***x***						
Oral hygiene/ Behavioral modification			***x***						***x***
Maintenance *(Tooth Cleaning)*									***x***
Inflammatory Markers (CRP, IL-6)		***x***			***x***		***x***		***x***
Oxidative stress (F2 isoprostanes, isofurans)		***x***			***x***		***x***		***x***
Nutritional Markers (Albumin)		***x***			***x***		***x***		***x***

Standard Protocol timepoints and items based on SPIRIT guidelines.

	STUDY PERIOD								
		Enrollment Baseline	**Post-allocation**						**Close-out**
TIMEPOINT**	$-t_2$		t_0	t_1	t_2	t_3	t_4	t_5	t_6
Nephrology Pre-screening	X								
Informed Consent		X							
Periodontal Screening		X							
Allocation		X							
INTERVENTIONS:									
Arm 1: Repeated Interventions + Behavioral Modification									
Arm 2: Control/Standard of Care			X						X
ASSESSMENTS:									
Demographic Data		X							
Biochemical Data		X							

Inflammatory Markers		X			X		X		X
Oxidative Stress Markers		X			X		X		X
Nutritional Markers		X			X		X		X
OHIP-14		X			X		X		X
Periodontal Parameters		X			X		X		X
Adverse Events				X					

[Provide a detailed timetable scheduling all aspects of the research. This will include data collection (e.g. time taken to administer questionnaires, complete interviews, abstract data from charts), analyze data, write reports etc. You may reference an attached flow diagram, including expected start and completion dates, and/or describe the time table here]:

- Expected Start Date: May 2016

General Time Table**:**
6-months: Complete the regulatory requirements, present the protocol in our recruitment sites and start recruitment.
12-months: Complete recruitment and treatment of 20 patients-Collect and transfer blood samples to the lab.
18-months: Complete recruitment and treatment of 20 patients-collect and transfer blood samples to the lab.
24-months: Complete follow-ups, perform biomarker lab analyses, compile and analyze data.

- Expected Completion Date: November 2018

6. Budget / resources: [You need to think about what you will need for your research and whether those resources are available to you. The IRB will want to know that you have thought carefully about what resources are needed and from where you expect to obtain these, and whether or not a budget workbook needs to be completed. Some types of research are more resource intensive/expensive than others and you will have to consider this when deciding upon your research method.]: The NIH budget is attached**.**

7. Dissemination [Describe how you intend to disseminate the results of your research, e.g. dissertation, presentation, web site, journal article.**]**: **The results of this research project will be presented in national and international meetings as well as in a form of peer-review journal article as expected by NIH.**

8. References / Literature Review:

1. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366(9499):1809-20.

2. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of Periodontitis in Adults in the United States: 2009 and 2010. Journal of dental research 2012;91(10):914-20.
3. Ioannidou E, Hall Y, Swede H, Himmelfarb J. Periodontitis associated with chronic kidney disease among Mexican Americans. Journal of public health dentistry 2012.
4. Kshirsagar AV, Moss KL, Elter JR, et al. Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk In Communities (ARIC) study. American journal of kidney diseases : the official journal of the National Kidney Foundation 2005;45(4):650-7.
5. Ioannidou E, Swede H. Disparities in Periodontitis Prevalence among Chronic Kidney Disease Patients. Journal of Dental Research 2011;90(6):730-34.
6. Akar H, Akar GC, Carrero JJ, Stenvinkel P, Lindholm B. Systemic consequences of poor oral health in chronic kidney disease patients. Clinical journal of the American Society of Nephrology : CJASN 2011;6(1):218-26.
7. Fisher MA, Taylor GW, Papapanou PN, Rahman M, Debanne SM. Clinical and serologic markers of periodontal infection and chronic kidney disease. J Periodontol 2008;79(9):1670-8.
8. Kshirsagar AV, Craig RG, Moss KL, et al. Periodontal disease adversely affects the survival of patients with end-stage renal disease. Kidney Int 2009;75(7):746-51.
9. Fisher MA, Taylor GW, Shelton BJ, et al. Periodontal disease and other nontraditional risk factors for CKD. Am J Kidney Dis 2008;51(1):45-52.
10. Fisher MA, Taylor GW, West BT, McCarthy ET. Bidirectional relationship between chronic kidney and periodontal disease: a study using structural equation modeling. Kidney international 2011;79(3):347-55.
11. Ioannidou E, Swede H, Dongari-Bagtzoglou A. Periodontitis Predicts Elevated C-reactive Protein Levels in Chronic Kidney Disease. Journal of dental research 2011;90(12):1411-5.
12. Ioannidou E, Swede H, Fares G, Himmelfarb J. Tooth Loss Strongly Associates With Malnutrition in Chronic Kidney Disease. Journal of periodontology 2013.
13. Ebersole JL, Cappelli D, Mathys EC, et al. Periodontitis in humans and non-human primates: oral-systemic linkage inducing acute phase proteins. Ann Periodontol 2002;7(1):102-11.
14. AAP. Treatment of plaque-induced gingivitis, chronic periodontitis, and other clinical conditions. Journal of periodontology. 2002/01/29 ed; 2001. p. 1790-800.
15. Tonetti MS, D'Aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. N Engl J Med 2007;356(9):911-20.
16. Wehmeyer MM, Kshirsagar AV, Barros SP, et al. A randomized controlled trial of intensive periodontal therapy on metabolic and inflammatory markers in patients With ESRD: results of an exploratory study. Am J Kidney Dis 2013;61(3):450-8.
17. Yazdi FK, Karimi N, Rasouli M, Roozbeh J. Effect of nonsurgical periodontal treatment on C-reactive protein levels in maintenance hemodialysis patients. Ren Fail 2013;35(5):711-7.
18. Banerjee T, Kim SJ, Astor B, et al. Vascular access type, inflammatory markers, and mortality in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis 2014;64(6):954-61.
19. Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 2005;293(14):1737-45.
20. Stenvinkel P, Carrero JJ, Axelsson J, et al. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol 2008;3(2):505-21.
21. Carrero JJ, Stenvinkel P. Inflammation in end-stage renal disease--what have we learned in 10 years? Semin Dial 2010;23(5):498-509.
22. Himmelfarb J. Oxidative stress in hemodialysis. Contrib Nephrol 2008;161:132-7.
23. Himmelfarb J, Ikizler TA, Ellis C, et al. Provision of antioxidant therapy in hemodialysis (PATH): a randomized clinical trial. J Am Soc Nephrol 2014;25(3):623-33.
24. Miyamoto T, Carrero JJ, Stenvinkel P. Inflammation as a risk factor and target for therapy in chronic kidney disease. Curr Opin Nephrol Hypertens 2011;20(6):662-8.
25. Stenvinkel P. Inflammation as a target for improving health in chronic kidney disease. F1000 Med Rep 2010;2:88.

26. Friedman AN, Moe SM, Perkins SM, Li Y, Watkins BA. Fish consumption and omega-3 fatty acid status and determinants in long-term hemodialysis. Am J Kidney Dis 2006;47(6):1064-71.
27. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360(14):1395-407.
28. Gamboa JL, Pretorius M, Todd-Tzanetos DR, et al. Comparative effects of angiotensin-converting enzyme inhibition and angiotensin-receptor blockade on inflammation during hemodialysis. J Am Soc Nephrol 2012;23(2):334-42.
29. Kaysen GA. Biochemistry and biomarkers of inflamed patients: why look, what to assess. Clin J Am Soc Nephrol 2009;4 Suppl 1:S56-63.
30. Seliger SL. Comorbidity and confounding in end-stage renal disease. Kidney Int 2010;77(2):83-5.
31. Snaedal S, Heimburger O, Qureshi AR, et al. Comorbidity and acute clinical events as determinants of C-reactive protein variation in hemodialysis patients: implications for patient survival. Am J Kidney Dis 2009;53(6):1024-33.
32. Carrero JJ, Stenvinkel P. Persistent inflammation as a catalyst for other risk factors in chronic kidney disease: a hypothesis proposal. Clin J Am Soc Nephrol 2009;4 Suppl 1:S49-55.
33. Borrell LN, Papapanou PN. Analytical epidemiology of periodontitis. J Clin Periodontol 2005;32 Suppl 6:132-58.
34. Peter KP, Mute BR, Doiphode SS, et al. Association between periodontal disease and chronic obstructive pulmonary disease: a reality or just a dogma? J Periodontol 2013;84(12):1717-23.
35. Scher JU, Bretz WA, Abramson SB. Periodontal disease and subgingival microbiota as contributors for rheumatoid arthritis pathogenesis: modifiable risk factors? Curr Opin Rheumatol 2014;26(4):424-9.
36. Kebschull M, Demmer RT, Papapanou PN. "Gum bug, leave my heart alone!"--epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. J Dent Res 2010;89(9):879-902.
37. Ide M, Papapanou PN. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes--systematic review. J Periodontol 2013;84(4 Suppl):S181-94.
38. Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. J Periodontol 2013;84(4 Suppl):S8-S19.
39. Naugle K, Darby ML, Bauman DB, Lineberger LT, Powers R. The oral health status of individuals on renal dialysis. Annals of periodontology / the American Academy of Periodontology 1998;3(1):197-205.
40. Franek E, Blaschyk R, Kolonko A, et al. Chronic periodontitis in hemodialysis patients with chronic kidney disease is associated with elevated serum C-reactive protein concentration and greater intima-media thickness of the carotid artery. Journal of nephrology 2006;19(3):346-51.
41. Chen LP, Chiang CK, Chan CP, Hung KY, Huang CS. Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients? American journal of kidney diseases : the official journal of the National Kidney Foundation 2006;47(5):815-22.
42. Craig RG, Kotanko P. Periodontitis and the end-stage renal disease patient receiving hemodialysis maintenance therapy. Compendium of continuing education in dentistry 2009;30(8):544, 46-52.
43. Grubbs V, Plantinga LC, Tuot DS, Powe NR. Chronic kidney disease and use of dental services in a United States public healthcare system: a retrospective cohort study. BMC nephrology 2012;13:16.
44. Tomas I, Marinho JS, Limeres J, et al. Changes in salivary composition in patients with renal failure. Archives of oral biology 2008;53(6):528-32.
45. Vaziri ND, Wong J, Pahl M, et al. Chronic kidney disease alters intestinal microbial flora. Kidney international 2013;83(2):308-15.
46. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol 2008;3(5):1526-33.
47. Stenvinkel P, Heimburger O, Jogestrand T, Karnell A, Samuelsson A. Does persistent infection with Chlamydia pneumoniae increase the risk of atherosclerosis in chronic renal failure? Kidney Int 1999;55(6):2531-2.

48. Chia S, Karim M, Elwood RK, FitzGerald JM. Risk of tuberculosis in dialysis patients: a population-based study. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 1998;2(12):989-91.
49. Simon TA, Paul S, Wartenberg D, Tokars JI. Tuberculosis in hemodialysis patients in New Jersey: a statewide study. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 1999;20(9):607-9.
50. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international 2006;69(11):1945-53.
51. Hewison M. An update on vitamin D and human immunity. Clinical endocrinology 2012;76(3):315-25.
52. Stenvinkel P. Inflammation in end-stage renal disease: the hidden enemy. Nephrology (Carlton) 2006;11(1):36-41.
53. Lockhart PB, Bolger AF, Papapanou PN, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. Circulation 2012;125(20):2520-44.
54. Noack B, Genco RJ, Trevisan M, et al. Periodontal infections contribute to elevated systemic C-reactive protein level. J Periodontol 2001;72(9):1221-7.
55. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005;76(11 Suppl):2106-15.
56. Ebersole JL, Cappelli D. Acute-phase reactants in infections and inflammatory diseases. Periodontol 2000 2000;23:19-49.
57. Chen LP, Chiang CK, Peng YS, et al. Relationship between periodontal disease and mortality in patients treated with maintenance hemodialysis. Am J Kidney Dis 2011;57(2):276-82.
58. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med 1965;58:295-300.
59. Stenvinkel P, Heimburger O, Jogestrand T. Elevated interleukin-6 predicts progressive carotid artery atherosclerosis in dialysis patients: association with Chlamydia pneumoniae seropositivity. Am J Kidney Dis 2002;39(2):274-82.
60. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol 2007;78(7 Suppl):1387-99.
61. Talbert J, Elter J, Jared HL, et al. The effect of periodontal therapy on TNF-alpha, IL-6 and metabolic control in type 2 diabetics. J Dent Hyg 2006;80(2):7.
62. Elter JR, Hinderliter AL, Offenbacher S, et al. The effects of periodontal therapy on vascular endothelial function: a pilot trial. Am Heart J 2006;151(1):47.
63. Ide M, Jagdev D, Coward PY, et al. The short-term effects of treatment of chronic periodontitis on circulating levels of endotoxin, C-reactive protein, tumor necrosis factor-alpha, and interleukin-6. J Periodontol 2004;75(3):420-8.
64. Yamazaki K, Honda T, Oda T, et al. Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine levels in Japanese periodontitis patients. J Periodontal Res 2005;40(1):53-8.
65. D'Aiuto F, Nibali L, Parkar M, Suvan J, Tonetti MS. Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol. J Dent Res 2005;84(3):269-73.
66. Lindhe J, Westfelt E, Nyman S, Socransky SS, Haffajee AD. Long-term effect of surgical/non-surgical treatment of periodontal disease. Journal of clinical periodontology 1984;11(7):448-58.
67. Axelsson P, Lindhe J. Effect of controlled oral hygiene procedures on caries and periodontal disease in adults. Results after 6 years. Journal of clinical periodontology 1981;8(3):239-48.
68. Wilson TG, Jr., Glover ME, Malik AK, Schoen JA, Dorsett D. Tooth loss in maintenance patients in a private periodontal practice. Journal of periodontology 1987;58(4):231-5.
69. Healthy People US. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. Healthy People 2020. Washington, DC: 2020. "http://www.healthypeople.gov. Accessed June 20, 2012 2012.

70. Probstfield JL, Frye RL. Strategies for recruitment and retention of participants in clinical trials. JAMA : the journal of the American Medical Association 2011;306(16):1798-9.
71. Cohen. Statistical power analysis for the behavioral sciences. 2nd. ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
72. van Manen JG, Korevaar JC, Dekker FW, et al. How to adjust for comorbidity in survival studies in ESRD patients: a comparison of different indices. Am J Kidney Dis 2002;40(1):82-9.
73. Honda H, Qureshi AR, Heimburger O, et al. Serum albumin, C-reactive protein, interleukin 6, and fetuin a as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis 2006;47(1):139-48.
74. Himmelfarb J. Linking oxidative stress and inflammation in kidney disease: which is the chicken and which is the egg? Semin Dial 2004;17(6):449-54.
75. Clancy C, Collins FS. Patient-Centered Outcomes Research Institute: the intersection of science and health care. Science translational medicine 2010;2(37):37cm18.
76. Locker D. Measuring oral health: a conceptual framework. Community dental health 1988;5(1):3-18.
77. Shanbhag S, Dahiya M, Croucher R. The impact of periodontal therapy on oral health-related quality of life in adults: a systematic review. Journal of clinical periodontology 2012;39(8):725-35.
78. Ohrn K, Jonsson B. A comparison of two questionnaires measuring oral health-related quality of life before and after dental hygiene treatment in patients with periodontal disease. International journal of dental hygiene 2012;10(1):9-14.
79. Guzeldemir E, Toygar HU, Tasdelen B, Torun D. Oral health-related quality of life and periodontal health status in patients undergoing hemodialysis. Journal of the American Dental Association 2009;140(10):1283-93.
80. Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community dental health 1994;11(1):3-11.
81. Joss A, Adler R, Lang NP. Bleeding on probing. A parameter for monitoring periodontal conditions in clinical practice. Journal of clinical periodontology 1994;21(6):402-8.
82. Chertow GM, Goldstein-Fuchs DJ, Lazarus JM, Kaysen GA. Prealbumin, mortality, and cause-specific hospitalization in hemodialysis patients. Kidney Int 2005;68(6):2794-800.
83. Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. American journal of kidney diseases : the official journal of the National Kidney Foundation 2001;37(1 Suppl 2):S66-70.
84. Fouque D, Pelletier S, Mafra D, Chauveau P. Nutrition and chronic kidney disease. Kidney Int 2011;80(4):348-57.
85. SPSS I. IBM SPSS Missing Values 22. Chicago, IL: IBM Corporation; 2014.
86. Heck RH TS, Tabata LN,. Multilevel and longitudinal modeling with IBM SPSS (2nd ed). New York: Rouledge Press; 2014.
87. Tabachnick BG FL. Using multivariate statistics. 5th. ed. New York, NY: Allyn &Bacon; 2007.
88. Cohen. Applied multiple regression/correlation analysis for the behavioral sciences. 2nd. ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1983.
89. Locker D, Matear D, Stephens M, Lawrence H, Payne B. Comparison of the GOHAI and OHIP-14 as measures of the oral health-related quality of life of the elderly. Community Dent Oral Epidemiol 2001;29(5):373-81.
90. Becker W, Berg L, Becker BE. The long term evaluation of periodontal treatment and maintenance in 95 patients. The International journal of periodontics & restorative dentistry 1984;4(2):54-71.
91. Ramfjord SP, Caffesse RG, Morrison EC, et al. Four modalities of periodontal treatment compared over five years. Journal of periodontal research 1987;22(3):222-3.
92. Badersten A, Nilveus R, Egelberg J. Effect of nonsurgical periodontal therapy (VIII). Probing attachment changes related to clinical characteristics. Journal of clinical periodontology 1987;14(7):425-32.

93. Axelsson P, Nystrom B, Lindhe J. The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. Journal of clinical periodontology 2004;31(9):749-57.
94. Spillane V, Byrne MC, Byrne M, et al. Monitoring treatment fidelity in a randomized controlled trial of a complex intervention. J Adv Nurs 2007;60(3):343-52.
95. Haffajee AD, Cugini MA, Dibart S, et al. Clinical and microbiological features of subjects with adult periodontitis who responded poorly to scaling and root planing. Journal of clinical periodontology 1997;24(10):767-76.
96. Cugini MA, Haffajee AD, Smith C, Kent RL, Jr., Socransky SS. The effect of scaling and root planing on the clinical and microbiological parameters of periodontal diseases: 12-month results. Journal of clinical periodontology 2000;27(1):30-6.
97. Preshaw PM, Holliday R, Law H, Heasman PA. Outcomes of non-surgical periodontal treatment by dental hygienists in training: impact of site- and patient-level factors. International journal of dental hygiene 2013;11(4):273-9.
98. Raudenbush SW BA, Cheong AS, Fai YF, Congdon RT, duToit M,. HLM 7: Hierarchical Linear and Nonlinear Modeling. Lincolnwood, IL: Scientific Software International; 2011.
99. Behle JH, Sedaghatfar MH, Demmer RT, et al. Heterogeneity of systemic inflammatory responses to periodontal therapy. J Clin Periodontol 2009;36(4):287-94.