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Publication Date

2017-02-01

DOI

10.1016/j.cct.2016.12.017

Peer reviewed

HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2018 November 15.

Published in final edited form as:

Contemp Clin Trials. 2017 February ; 53: 143–150. doi:10.1016/j.cct.2016.12.017.

The Kidney and Periodontal Disease (KAPD) study: A pilot randomized controlled trial testing the effect of non-surgical periodontal therapy on chronic kidney disease

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Abstract

Introduction: Chronic kidney disease (CKD) remains a prevalent public health problem that disproportionately affects minorities and the poor, despite intense efforts targeting traditional risk factors. Periodontal diseases are common bacterial plaque-induced inflammatory conditions that

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can respond to treatment and have been implicated as a CKD risk factor. However there is limited evidence that treatment of periodontal disease slows the progression of CKD.

Methods/design: We describe the protocol of the Kidney and Periodontal Disease (KAPD) study, a 12-month unblinded, randomized, controlled pilot trial with two intent-to-treat treatment arms: 1. immediate intensive nonsurgical periodontal treatment or 2. rescue treatment with delayed intensive treatment. The goals of this pilot study are to test the feasibility of conducting a larger trial in an ethnically and racially diverse, underserved population (mostly poor and/or low literacy) with both CKD and significant periodontal disease to determine the effect of intensive periodontal treatment on renal and inflammatory biomarkers over a 12-month period.

Results: To date, KAPD has identified 634 potentially eligible patients who were invited to in-person screening. Of the 83 (13.1%) of potentially eligible patients who attended in-person screening, 51 (61.4%) were eligible for participation and 46 enrolled in the study. The mean age of participants is 59.2 years (range 34 to 73). Twenty of the participants (43.5%) are Black and 22 (47.8%) are Hispanic.

Discussion: Results from the KAPD study will provide needed preliminary evidence of the effectiveness of nonsurgical periodontal treatment to slow CKD progression and inform the design future clinical research trials.

Keywords

(max 6) chronic kidney disease; Periodontal disease; Non-surgical periodontal disease treatment; Periodontitis; oral health

1. Introduction

Chronic kidney disease (CKD) remains a public health problem that disproportionately affects poor and minority populations. Disparities in CKD progression are a particular concern. Blacks and Hispanics, for example, have a 3.0-fold and 1.4-fold increased risk respectively of progressing to end-stage kidney disease when compared to their White counterparts [1].

Similarly, periodontal diseases affect poor and minority populations disproportionately. While the estimated prevalence of periodontal disease among US adults is 46% overall, it is 63.5% in Hispanics, 59.1% in Blacks and 63.7% in those living below 100% of the federal poverty line [2]. A systematic review of 88 studies in 125 populations estimated that 56.8% of adults on dialysis and 31.6% of those with less severe CKD had periodontal disease [3].

While periodontal disease can be prevented and managed through regular dental care, N85 million persons in the United States age 18 years and older have no form of dental insurance, and Medicaid coverage for adult dental services varies from state to state [4,5]. We found that only 15% of patients in an urban public hospital setting (San Francisco Community Health Network) had a dental visit during a 4-year period of observation, and those with CKD had a 27% lower likelihood of a dental visit than those without CKD [6]. In a national survey, we found that less than half of minority and poor populations reported access to recommended dental care [7]. These findings suggest that disparities in the

treatment of periodontal disease may be an important yet underutilized intervention that, in turn, may impact disparities in CKD.

Although several studies have implicated periodontal disease as a novel risk factor for CKD progression [8–11], studies to determine the extent to which treatment of periodontal disease alters the trajectory of kidney function decline are limited, with none conducted in the United States. One large population-based observational study using Taiwanese insurance claim data found that patients with periodontal disease who received periodontal treatment consisting of subgingival curettage and/or periodontal flap surgery had a 40% lower likelihood of incident end-stage renal disease (ESRD) as defined by ICD-9 codes than those who did not undergo those procedures [12]. However, to date there have only been two clinical trials examining the effect of periodontal treatment on kidney function. In an Italy-based study, Graziani and colleagues found a statistically significant decrease in cystatin C levels among 20 systemically healthy adults 3 months after non-surgical periodontal treatment, but the creatinine-based estimated glomerular filtration rate (eGFR) did not change [13]. In Brazil, Artese and colleagues found 21 patients with CKD and 19 without CKD had improved eGFR 3 months after periodontal treatment (mean change 4.2 and 13.6 ml/min/1.73 m^2, respectively) [14]. However neither of these small trials included randomization or repeated periodontal treatment, and both trials had a short follow-up period.

Therefore, randomized clinical trial data among populations disproportionately affected by kidney and periodontal disease are needed to determine the potential impact of periodontal treatment on kidney function decline over an extended period of time. We developed the Kidney and Periodontal Disease (KAPD) study to address this need. The purpose of this paper is to describe the details of this study design and recruitment efforts to date.

2. Methods

2.1. Study design/overview

The Kidney and Periodontal Disease (KAPD) study is a single center un-blinded, randomized controlled pilot trial with 2 intent-to-treat arms: immediate intensive periodontal treatment or 2. rescue treatment only with intensive periodontal treatment at the end of the study. The University of California, San Francisco (UCSF) Institutional Review Board approved the protocol.

Participants are being randomly assigned to each arm and evaluated at baseline and at 4,8, and 12 months following randomization for repeat periodontal assessment and measures of various renal and inflammatory biomarkers (Fig. 1 and Table 1). The goals of this study are to test the feasibility of conducting this trial among a high-risk (mostly poor and racial/ethnic minority) population, and to obtain preliminary estimates of the magnitude of the effect and variability in renal and inflammatory biomarkers in response to intensive periodontal treatment over a 12-month period among participants with both CKD and periodontal disease. We hypothesize that this study is feasible and that intensive periodontal intervention will slow the progression of CKD as measured by renal biomarkers compared to the non-intensive treatment group.

2.2. Inclusion criteria

KAPD includes English and Spanish-speaking individuals 20– 75 years old, who are currently receiving primary care within the San Francisco Community Health Network. Patients with CKD [defined by at least two estimated glomerular filtration rate (eGFR) measurements (using the Modification of Diet in Renal Disease (MDRD) equation as reported by the clinical laboratory) in last 12 months between 15 and 60 ml/min/1.73 m^2 at time of screening] who are not on dialysis; have no evidence of recent recovering acute kidney injury (a documented eGFR increase by N50% in last 6 months); have at least 6 teeth at baseline; have no severe dental disease defined as deep dental caries, endodontic involvement of one or more teeth, presence of abscesses of periodontal or endodontic origin, or dental conditions requiring immediate treatment or any hard or soft tissue lesion requiring further evaluation and/or treatment; and moderate to severe periodontal disease are invited to participate in the study (Table 2). The oral screening included visual examination and assessment of pocket probing depths, position of gingival margin used to calculate clinical attachment loss, and bleeding on probing are recorded for each tooth at 6 sites per tooth (mesial buccal, buccal, distal buccal, mesial lingual, lingual, and distal-lingual). Plaque levels are recorded for each tooth on the buccal and lingual aspect of each tooth.

Periodontal disease is defined by the Centers for Disease Control/ American Academy of Periodontology (CDC/AAP) 2003 consensus definition [15] and by extent of bleeding on probing. According to the CDC/ AAP criteria moderate periodontal disease is defined as 2 or more interproximal sites with ≥4 mm clinical attachment loss (not on the same tooth) or 2 or more interproximal sites with probing depth ≥ 5 mm, also not on the same tooth. Severe periodontal disease is defined as the presence of 2 or more interproximal sites with ≥6 mm clinical attachment loss (not on the same tooth) and 1 or more interproximal site(s) with ≥5 mm probing depth. In addition to meeting CDC/AAP criteria, participants must have bleeding on probing on at least 30% of examined sites. All patients found ineligible for study participation are provided a handout of local dentists and recommendation for care as needed.

2.3. Randomization

Participants are assigned in a 2:1 ratio to the immediate intensive non-surgical periodontal or rescue treatment with delayed intensive treatment groups by the study biostatistician using randomly permuted blocks of size 3. Randomization is stratified by presence of diabetes, to ensure balance on this strong risk factor for causing/accelerating both CKD and periodontal disease. Participants are informed of their randomization assignment at the baseline visit.

2.4. Periodontal intervention

The intensive periodontal treatment is adapted from the protocol described by Tonetti and colleagues [16]. All participants receive instruction in oral hygiene at baseline and 4-, 8-, and 12-month study visits. Participants assigned to the intensive periodontal treatment have full-mouth scaling and root planing (below the gumline deep cleaning treatment), local controlled-release antibiotic administration (minocycline HCl, Arestin® microspheres) in deeper gum pockets ≥5 mm, and recommendation for extraction of teeth that cannot be saved (hopeless teeth) at the baseline study visit. Hopeless teeth are defined as those with 2

or more of the following: [1] loss of over 75% of the supporting bone; [2] probing depths >8 mm; [3] class III furcation involvement; [4] class III mobility with tooth movement in lateral (bucco-lingual or mesio-distal) and vertical directions; [5] poor crown-root ratios; [6] root proximity with minimal interproximal bone and evidence of horizontal bone loss. Hopeless teeth are determined by one of the calibrated study dentists and confirmed based on Panorex X-rays at the baseline visit and, if clinically necessary, at the subsequent 4-, 8-, and/or 12-month study visits. Additional deep cleaning and antibiotic administration occur at study months 4 and 8 as needed for persistent gum disease. This antibiotic formulation was chosen because it is active against a broad spectrum of gram-negative and gram-positive anaerobes, including those implicated in adult periodontal diseases. Further, its controlled delivery platform (microspheres) gives up to 21 days of high concentrations of minocycline in the periodontal pockets without detectable systemic exposure [17]. Deep cleaning only at sites with progressive disease occurs at study month 12.

Given the relatively long, 12-month duration of the protocol, we considered it unethical to have a true control group with no periodontal treatment until study end. Therefore, participants assigned to rescue treatment also have extraction of hopeless teeth at the baseline visit and scaling and root planing without antibiotic administration at study months 4 and 8 only to sites with progressive periodontal disease (pockets which have increased by 3 mm or more in probing depth relative to prior examination). Full-mouth scaling and root planing with antibiotic administration to deeper gum pockets are performed at the 12-month study visit.

Dentists perform dental examinations. Prior to commencing examination of participants, a periodontist/calibrator/gold standard examiner (MR) conducted an orientation and calibration with the six other examining dentists to date. The orientation included a demonstration of techniques to conduct a systematic intraoral and extra oral examination of soft and hard tissues, assessment for decayed, missing and filled teeth (DMFT) and measures for gingival index (GI) [18], bleeding on probing (BOP), plaque index (PI) [19], gingival margin position (GM), and probing depths (PD). Following this demonstration, each examiner was assessed with the calibrator (MR) on a second participant for PD, GM to CEJ to calibrate tooth surfaces with clinical decay (caries), CAL, and GI. A minimum concurrence of 90% for surfaces with or without caries, PD, and GM position was required. If this level of concurrence was not achieved, the calibrator would review these techniques and conduct a second calibration on another patient until this minimal concurrence was met [20]. There was 97.6–100% concurrence of probing depth assessments within ±1 mm and 96.4–100% concurrence of gingival margins within ±1 mm between calibrator and examiners. Periodontists perform uncomplicated tooth extractions while complicated extractions are performed by an oral surgeon. The study dental hygienist performs scaling and root planing and antibiotic administration and provides instruction in oral hygiene. With the exception of uncomplicated tooth extractions, which are performed at the University of California, San Francisco Dental Center, all study activities take place at the Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG), a public hospital and site of all specialty care for patients in the San Francisco Community Health Network.

2.5. Recruitment

Under a waiver for screening of health records, potentially eligible participants are identified. Potentially eligible participants are initially identified by language, age, and eGFR criteria through electronic medical record extraction (The Health Record Data Service, THREDS) performed by Clinical Data Research Consultations, a service that extracts data sets from ZSFG data sources for research purposes. Study staff review electronic medical records (EMR) of identified patients to confirm that language, age, and eGFR criteria are met. Remaining potentially eligible participants are excluded if on dialysis, have evidence of recent acute kidney injury, are clinically inappropriate as defined below, have an allergy to tetracycline or minocycline, have a history of either infective endocarditis or a heart valve replaced or repaired with prosthetic material, or if the medication list includes anticoagulants (except aspirin, dipyridamole, or clopidogrel) or chronic immunosuppressive medications (not short-term use of prednisone for the treatment of gout or reactive airway disease). Patients with recent acute kidney injury (a documented eGFR increase by >50% in last 6 months) are excluded to avoid falsely attributing any improvements in renal biomarkers to the periodontal intervention. Patients are considered clinically inappropriate if the EMR have a condition that may preclude them from being able to participate in a 12-month study protocol, such as deceased, active illicit drug use, untreated psychosis, assaultive behavior, or metastatic malignancy. Patients with a history of either infective endocarditis, heart valve replacement or repair with prosthetic material are excluded because they require antibiotic prophylaxis, a treatment that is not part of the study protocol.

Patients who remain potentially eligible after EMR review are mailed an invitation letter to attend an in-person screening, which includes detailed explanation of the study protocol, obtaining written consent; confirmation of pre-screening allergies, medications, and medical condition criteria; and dental examination. Written consent is obtained prior to medical review and oral examination. A pregnancy test is performed on all women of childbearing age (18–50 years) at screening and each study visit. Women with a positive pregnancy test at screening are excluded. However, women who become pregnant during the study may still participate in KAPD, but no x-rays are performed and no antibiotics are given. Patients who meet dental criteria (at least 6 teeth, no condition requiring immediate intervention, and moderate or severe periodontal disease by CDC/AAP definition) are invited to participate in KAPD. All study inclusion and exclusion criteria are shown in Table 2.

Recruitment and retention strategies include a bilingual research staff; update of participant contact information at every study visit; communication with participants on a regular basis to ensure contact information is correct; a study raffle; and participant payment. Patients invited for in-person screening are paid $US10 cash, regardless of screening outcome. Enrolled participants receive Visa gift cards in the amounts of $US50 for baseline and 12-month study visits, and $US25 for 4- and 8-month study visits. Participants receive additional Visa gift cards for $US25 if extractions are required and $US50 if all 4 study visits are completed. Each participant receives free periodontal treatment, Panorex radiograph, and extractions as well as a sample bag of oral hygiene items at each study visit.

2.6. Measures

2.6.1. Primary outcomes—Blood and urine samples are collected at the baseline, 4-month, and 12-month study visits. In addition to measuring traditional markers of kidney function (serum creatinine), KAPD will measure markers of kidney structure as glomerular injury (albuminuria and serum neutrophil gelatinase-associated lipocalin (NGAL) and tubular injury (urine NGAL)); vascular endothelial injury (asymmetrical dimethylarginine (ADMA)); and systemic inflammation (Interleukin-6 and C-reactive protein) to both predict the effect of treatment and determine the specific mechanisms through which the periodontal pathogen may exert its effects.

2.6.2. Secondary outcomes—Since diabetes and smoking are strong risk factors for both periodontal disease and CKD [21–27], glycosylated hemoglobin (Hemoglobin A1c, HbA1c) and plasma cotinine are included as secondary measures. HbA1c is measured at baseline, 4-month, and 12-month study visits. Cotinine is measured at the baseline visit only.

Weight and blood pressure are measured at each study visit. Oral examinations are performed at all study visits and include determination of pocket probing depth and clinical attachment level at 6 sites per tooth, assessment of bleeding on probing, plaque index, and gingival index. Dental samples, including saliva, subgingival plaque, and gingival crevicular fluid, are collected at the baseline and 12-month study visits.

2.6.3. Self-report measures—Participants are asked to complete the short Test of Functional Health Literacy Assessment (sTOFHLA) at the baseline visit. All other self-report measures are obtained by study coordinator administered questionnaires. Socio-demographic information, including age, gender, race/ethnicity, education level, marital status, country of origin, languages spoken at home, and medical insurance, is ascertained at the baseline study visit. Health related behaviors (including oral health behaviors, tobacco use, and physical activity); comorbid conditions; medications (including dietary supplements); and interim medical and dental treatment are ascertained at each study visit.

KAPD study measures and schedule are summarized in Table 1.

2.7. Data analysis and sample size

We will calculate descriptive statistics as appropriate for each feasibility, process, and clinical outcome at each visit. Generalized linear mixed models (GLMMs) for repeated continuous, binary, and count outcomes will be used to assess treatment effects on study outcomes at 4, 8, and 12 months; the baseline outcome will be included in the analysis to control for any between-group differences at baseline, with treatment effects captured using time-by-treatment interactions. Outcomes will be transformed as needed to meet model assumptions, and random effects will be used to account for within-participant correlation of the outcomes. GLMMs for tooth-specific periodontal outcomes including pocket depth (PD), clinical attachment loss (CAL), and bleeding on probing (BOP), will include tooth and site as fixed effects, and account for the nested correlation of teeth within participant within occasion. Results will be considered statistically significant at a conventional two-sided $p < 0.05$.

The accrual target of 51 participants assigned 2:1 to intensive (n = 34) or rescue treatment (n = 17) is typical for a pilot study and feasible given available resources. In the overall sample, we will be able to estimate the means of feasibility and process outcomes within margins of sampling error (MSEs) of ±14 percentage points (ppts) for binary measures and 0.28 standard deviations (SDs) for continuous ones; within the treated group, corresponding MSEs will be 18 ppts and 0.35 SDs. In providing preliminary estimates to inform sample size calculations for a definitive trial, we will be able to estimate the net effect of intensive versus delayed intensive periodontal treatment on CKD biomarkers at 12 months within MSEs of 0.35–0.51 SDs, depending on the degree of within subject correlation, after accounting for loss to follow-up of 20% of participants by 12 months.

2.8. Data and safety monitoring

The study coordinator monitors adverse events continually and completes an adverse event form with each participant at the start of their baseline, 4-, 8- and 12-month study visits. All adverse events are reported to the Principal Investigator (PI). Reportable adverse events are submitted to the Institutional Review Board per established policy. The PI (VG) receives and reviews adverse events individually as they occur, and in aggregate on a monthly basis across the entire study population. Bleeding following scaling and root planing and extractions are monitored for a period of 10 min. Participants are instructed to call the study coordinator, PI, or to report to the emergency room if significant bleeding occurs following dismissal. Participants are monitored in the clinic during periodontal treatment for signs of allergy and are asked to notify the study coordinator of any delayed adverse reactions to the antibiotics following dismissal.

A Data Safety Monitoring Board (DSMB) consisting of three members, who are experts in or representatives of the fields of chronic kidney disease, periodontal disease, clinical trial methodology, biostatistics, epidemiology, and disparities research, was assembled. The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) approved all members. Membership consists of persons completely independent of the investigators and have no financial, scientific or other conflict of interest with the trial. Each DSMB member signed written documentation attesting to absence of a conflict of interest. The DSMB responsibilities are to focus on trial site performance, participant safety, and treatment effects.

3. Results

KAPD has been actively enrolling since February 2014. To date, 2860 EMR records have been screened, identifying 634 (22.2%) potentially eligible patients who were invited to in-person screening. Of the 2226 patients who were not eligible after EMR screening, 1425 (64.0%) did not meet eGFR criteria (did not have CKD or was on dialysis) and 623 (28.0%) were deemed clinically inappropriate. Of the 634 potentially eligible patients, we were unable to reach 346 (54.6%), 113 declined in-person invitation (17.8%), and 83 (13.1%) attended the in-person screening. Nearly two-thirds (n = 51, 61.4%) of those who attended in-person screening were eligible for participation. Of the 32 ineligible patients, 29 (90.6%)

were excluded for not meeting periodontal disease severity criteria. Additional details are shown in Fig. 2.

Fifty-one patients were randomized (34 to Intensive and 17 to Rescue), but 5 were lost to follow-up before the baseline visit (4 Intensive and 1 Rescue). We considered patients who attended the baseline visit as enrolled (n = 46). Five patients dropped out of the study after enrollment (2 intervention, 3 rescue only) and 17 have completed the study.

Of the 46 enrolled patients, 31 (67.4%) are male, 20 (43.5%) Black, 10 (21.7%) Hispanic, 22 (47.8%) have diabetes, and 23.9 (%) are current smokers. The mean age of study participants is 59.2 years (range 34 to 73). Baseline dental measures are shown in Table 3.

We have adjusted recruitment procedures. The initial recruitment letter offered no financial incentive for in-person screening and specified, “You may be able to take part in this study if you: …have chronic kidney disease…have moderate to severe periodontal (gum) disease.” When the study coordinator called patients to follow-up on the letter, many refused in-person screening stating that they did not have CKD or periodontal disease. We revised the letter to offer US$10 for travel expenses and a raffle entry to win a $75 gift card and included more vague language, stating only that KAPD is a research study “to understand how dental health affects kidney function.” These changes resulted in an 11% increase in the proportion of patients who attended in-person screening.

For a two-week period we posted a study flyer at the ZSFG study site elevators and in the general medicine, family medicine, and oral surgery clinics. We abandoned this recruitment tactic because of the 38 patients who called the study coordinator and gave oral consent to review their EMR, none were eligible to be invited to in-person screening (35 did not have CKD, 1 was on dialysis, and 1 had active drug use).

KAPD has had several challenges. With the exception of tooth extractions, the periodontal treatment takes place in the busy ZSFG oral surgery clinic because there is no dental clinic there. As a result, KAPD is restricted to a single treatment chair, two days per week.

Hopeless tooth extraction has also been a challenge. Of the 24 participants who have completed the 4-month study visit, 11 (46%) had one or more hopeless teeth. Roughly half of these participants (n = 6, 54%) had only 1 or 2 hopeless teeth and 4 participants had between 6 and 9 hopeless teeth. Six participants completed extractions by the 4month study visit, including 2 participants with 6 or more hopeless teeth. Several factors contributed to hopeless tooth extraction delay or failure including change in site performing extractions after study start when we realized the ZSFG oral surgery clinic could not accommodate uncomplicated extractions; some participants were fearful of extractions; and some participants were unwilling to have extraction unless the study paid for dental replacement.

4. Discussion

To our knowledge, upon completion KAPD will be the first RCT in an ethnically and racially diverse population disproportionately affected by periodontal disease and CKD. Although this is a pilot study with a recruitment goal of 51 patients and a 12-month study

protocol, KAPD will be the largest and longest RCT examining the effect of periodontal disease treatment on CKD progression to date. The data obtained from this pilot study will be used to refine the recruitment strategy and intervention protocol for a larger randomized controlled trial. Additionally, the magnitude of treatment effect and variability data obtained from biomarker measurements will inform the sample size needed to definitively test the effect of periodontal disease treatment on CKD progression.

Given that the potential pathophysiologic mechanism(s) of periodontal pathogen injury to renal tissue have not been established and that little change in traditional markers of kidney function (e.g. creatinine and eGFR) is expected over the 12-month study protocol, KAPD measurements include novel biomarkers of kidney structure and function. NGAL is a small 25-kDa protein released into the blood and urine from kidney tubular cells after harmful stimuli. Initially described as a marker for acute kidney injury, strong evidence suggests NGAL is a distinct marker for CKD progression as well [28]. A cross-sectional study of 80 patients with CKD stages 2–4, showed that serum NGAL was elevated, particularly among those with the most advanced CKD [29]. Serum and urinary NGAL have been shown to be elevated in cross-sectional studies of patients with IgA nephropathy [30], polycystic kidney disease [31], pediatric lupus nephritis [32], and CKD [33]. Further, baseline serum and urinary NGAL were predictors of eGFR decline in a longitudinal study of 96 patients with CKD over a median follow-up of 18.5 months [34]. KAPD has also banked serum and urine samples. This will allow measurement biomarkers that have emerged since KAPD was designed. For example, Kidney Injury Molecule-1 (KIM-1) has emerged as a promising biomarker for CKD progression [35,36].

As has been demonstrated in cardiovascular literature [37], endothelial injury in the kidney may be a pathway by which periodontal pathogens lead to disease progression. Therefore, we will also measure ADMA as a biomarker of endothelial dysfunction. ADMA is an endogenous inhibitor of nitric oxide synthase (which converts the amino acid L-arginine into nitric oxide), thus inhibiting key roles of nitric oxide in vascular homeostasis [38]. ADMA is elevated in CKD [39] and in settings of increases oxidative stress, such as periodontal disease [40]. ADMA is also a marker of CKD progression. In a study of incident CKD patients followed prospectively, ADMA was inversely correlated with GFR and was a predictor of progression to ESRD [41]. In another study of early CKD in patients with type 1 diabetes, increased ADMA levels predicted the development and progression of nephropathy [42]. Of note, ADMA is highly inversely correlated with brachial flow-mediated dilatation (FMD) [43], which was measured by Tonetti et al. [16] as a marker of endothelial function; but unlike ADMA, measuring FMD is technically difficult, time-consuming, and cost-prohibitive [44].

KAPD is not without limitations and challenges. One, KAPD is unblinded because neither examiners nor participants could truly be blinded as to whether participants had intensive periodontal treatment or not, in the same way a study radiologist could not be blinded to whether or not an organ was surgically removed on CT scan examination. However, study examiners never performed the periodontal treatment and the study hygienist never performed oral examinations. Two, the nature of this study population and the public hospital setting for study activities have presented numerous and institutional level

challenges for KAPD recruitment and retention. For example, disconnected phone numbers and loss of housing are not uncommon and in-person recruitment rather than a letter invitation may have been more effective in a highly racially and ethnically diverse population. Further, limited resources are a barrier to extraction of hopeless teeth and prevent all study activities from taking place at one site, thus potentially compromising study retention. Three, the lack of a true control group will likely narrow separation of treatment groups.

Current efforts to slow progression of CKD focus on modification of traditional risk factors that require a complex—and infrequently achieved—combination of appropriate provider disease management, behavioral change, self-monitoring, and medication adherence to achieve sustained impact. On the other hand, periodontal disease may be a novel risk factor that can be treated in a dental office through removal of bacterial deposits through scaling and root planing, local administration of antibiotics to deeper periodontal disease sites, plaque control instruction, and maintenance visits 2–4 times per year to remove new bacterial deposits and monitor the periodontal condition. Therefore, KAPD is at the forefront of integrating oral health into our general medicine approach to disease management, potentially contributing to redefining the approach to CKD management and to advance dental health policy in the United States. Given the disproportionate lack of access to dental care and high prevalence of periodontal disease among the population targeted by KAPD, these findings may lead to the treatment of periodontal disease as an important and currently underutilized intervention for reducing disparities in CKD.

Acknowledgements

KAPD and VG are supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, Bethesda, MD) [grant number 1K23DK093710–01A1] and by the Harold Amos Medical Faculty Development Program of the Robert Wood Johnson Foundation (P0045259), Princeton, NJ.

We thank the members of the DSMB: KL Johansen (chair), G. Armitage, and CE McCullough.

Disclosures

The study drug (minocycline HCl, Arestin® microspheres) was provided through an Investigator-initiated research grant from Valeant Pharmaceuticals, Bridgewater, NJ. DL is a member of the Abbvie-UCSF Steering Committee.

References

[1]. U.S. Renal Data System. USRDS, Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, Bethesda, 2015 (MD2015).

[2]. Eke PI, Dye BA, Wei L, et al., Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012, J. Periodontol 86 (2015) 611–622. [PubMed: 25688694]

[3]. Ruospo M, Palmer SC, Craig JC, et al., Prevalence and severity of oral disease in adults with chronic kidney disease: a systematic review of observational studies, Nephrol. Dial. Transplant 29 (2014) 364–375. [PubMed: 24081863]

[4]. McGinn-Shapiro M, Medicaid Coverage of Adult Dental Services, National Academy for State Health Policy, Portland, 2008.

[5]. (Accessed March 3, 2015, at) https://www.healthcare.gov/coverage/dentalcoverage/.

[6]. 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 Nephrol. 13 (16) (2012).

[7]. Grubbs V, Plantinga LC, Crews DC, et al., Vulnerable populations and the association between periodontal and chronic kidney disease, Clin. J. Am. Soc. Nephrol 6 (2011) 711–717. [PubMed: 21350109]

[8]. Iwasaki M, Taylor GW, Nesse W, Vissink A, Yoshihara A, Miyazaki H, Periodontal disease and decreased kidney function in Japanese elderly, Am. J. Kidney Dis 59 (2012) 202–209. [PubMed: 22001179]

[9]. Shultis WA, Weil EJ, Looker HC, et al., Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes, Diabetes Care 30 (2007) 306–311. [PubMed: 17259499]

[10]. Grubbs V, Vittinghoff E, Beck JD, et al., Association between periodontal disease and kidney function decline in African Americans: the Jackson heart study, J. Periodontol 86 (2015) 1126–1132. [PubMed: 26110451]

[11]. Grubbs V, Vittinghoff E, Taylor G, et al., The association of periodontal disease with kidney function decline: a longitudinal retrospective analysis of the MrOS dental study, Nephrol. Dial. Transplant 31 (2016) 466–472. [PubMed: 26320037]

[12]. Lee CF, Lin CL, Lin MC, Lin SY, Sung FC, Kao CH, Surgical treatment for patients with periodontal disease reduces risk of end-stage renal disease: a nationwide population-based retrospective cohort study, J. Periodontol 85 (2014) 50–56. [PubMed: 23646848]

[13]. Graziani F, Cei S, La Ferla F, Vano M, Gabriele M, Tonetti M, Effects of non-surgical periodontal therapy on the glomerular filtration rate of the kidney: an exploratory trial, J. Clin. Periodontol 37 (2010) 638–643. [PubMed: 20500539]

[14]. Artese HP, Sousa CO, Luiz RR, Sansone C, Torres MC, Effect of non-surgical periodontal treatment on chronic kidney disease patients, Braz. Oral Res 24 (2010) 449–454. [PubMed: 21180967]

[15]. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ, Update of the case definitions for population-based surveillance of periodontitis, J. Periodontol 83 (2012) 1449–1454. [PubMed: 22420873]

[16]. Tonetti MS, D'Aiuto F, Nibali L, et al., Treatment of periodontitis and endothelial function, N. Engl. J. Med 356 (2007) 911–920. [PubMed: 17329698]

[17]. Williams RC, Paquette DW, Offenbacher S, et al., Treatment of periodontitis by local administration of minocycline microspheres: a controlled trial, J. Periodontol 72 (2001) 1535–1544. [PubMed: 11759865]

[18]. Loe H, Silness J, Periodontal disease in pregnancy. I. Prevalence and severity, Acta Odontol. Scand 21 (1963) 533–551. [PubMed: 14121956]

[19]. Silness J, Loe H, Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition, Acta Odontol. Scand 22 (1964) 121–135. [PubMed: 14158464]

[20]. Moscicki AB, Yao TJ, Ryder MI, et al., The burden of oral disease among perinatally HIV-infected and HIV-exposed uninfected youth, PLoS One 11 (2016), e0156459.. [PubMed: 27299992]

[21]. Biesenbach G, Grafinger P, Janko O, Zazgornik J, Influence of cigarette-smoking on the progression of clinical diabetic nephropathy in type 2 diabetic patients, Clin. Nephrol 48 (1997) 146–150. [PubMed: 9342485]

[22]. Chavarry NG, Vettore MV, Sansone C, Sheiham A, The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis, Oral Health Prev. Dent 7 (2009) 107–127. [PubMed: 19583037]

[23]. Nelson RG, Shlossman M, Budding LM, et al., Periodontal disease and NIDDM in Pima Indians, Diabetes Care 13 (1990) 836–840. [PubMed: 2209317]

[24]. Orth SR, Ritz E, The renal risks of smoking: an update, Curr. Opin. Nephrol. Hypertens 11 (2002) 483–488. [PubMed: 12187311]

[25]. Ritz E, Orth SR, Nephropathy in patients with type 2 diabetes mellitus, N. Engl. J. Med 341 (1999) 1127–1133. [PubMed: 10511612]

[26]. Ritz E, Rychlik I, Locatelli F, Halimi S, End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions, Am. J. Kidney Dis 34 (1999) 795–808. [PubMed: 10561134]

[27]. Tonetti MS, Cigarette smoking and periodontal diseases: etiology and management of disease, Ann. Periodontol 3 (1998) 88–101. [PubMed: 9722693]

[28]. Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE, Biomarkers in chronic kidney disease: a review, Kidney Int. 80 (2011) 806–821. [PubMed: 21697815]

[29]. Malyszko J, Malyszko JS, Bachorzewska-Gajewska H, Poniatowski B, Dobrzycki S, Mysliwiec M, Neutrophil gelatinase-associated lipocalin is a new and sensitive marker of kidney function in chronic kidney disease patients and renal allograft recipients, Transplant. Proc 41 (2009) 158–161. [PubMed: 19249502]

[30]. Ding H, He Y, Li K, et al., Urinary neutrophil gelatinase-associated lipocalin (NGAL) is an early biomarker for renal tubulointerstitial injury in IgA nephropathy, Clin. Immunol 123 (2007) 227–234. [PubMed: 17360238]

[31]. Bolignano D, Coppolino G, Campo S, et al., Neutrophil gelatinase-associated lipocalin in patients with autosomal-dominant polycystic kidney disease, Am. J. Nephrol 27 (2007) 373–378. [PubMed: 17570904]

[32]. Brunner HI, Mueller M, Rutherford C, et al., Urinary neutrophil gelatinase-associated lipocalin as a biomarker of nephritis in childhood-onset systemic lupus erythematosus, Arthritis Rheum. 54 (2006) 2577–2584. [PubMed: 16868980]

[33]. Mitsnefes MM, Kathman TS, Mishra J, et al., Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in children with chronic kidney disease, Pediatr. Nephrol 22 (2007) 101–108. [PubMed: 17072653]

[34]. Bolignano D, Lacquaniti A, Coppolino G, et al., Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease, Clin. J. Am. Soc. Nephrol 4 (2009) 337–344. [PubMed: 19176795]

[35]. Bhavsar NA, Kottgen A, Coresh J, Astor BC, Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) as predictors of incident CKD stage 3: the Atherosclerosis Risk in Communities (ARIC) Study, Am. J. Kidney Dis 60 (2012) 233–240. [PubMed: 22542304]

[36]. Peralta CA, Katz R, Bonventre JV, et al., Associations of urinary levels of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) with kidney function decline in the Multi-Ethnic Study of Atherosclerosis (MESA), Am. J. Kidney Dis 60 (2012) 904–911. [PubMed: 22749388]

[37]. Amar S, Gokce N, Morgan S, Loukideli M, Van Dyke TE, Vita JA, Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation, Arterioscler. Thromb. Vasc. Biol 23 (2003) 1245–1249. [PubMed: 12763762]

[38]. Cooke JP, Asymmetrical dimethylarginine: the Uber marker? Circulation 109 (2004) 1813–1818. [PubMed: 15096461]

[39]. Aslam S, Santha T, Leone A, Wilcox C, Effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in end-stage renal disease patients on hemodialysis, Kidney Int. 70 (2006) 2109–2115. [PubMed: 17063175]

[40]. Thomopoulos C, Tsioufis C, Soldatos N, et al., Chronic periodontal disease and systemic inflammation on endothelial dysfunction in untreated hypertensive patients: Pp.2.53, J. Hypertens 28 (2010).

[41]. Ravani P, Tripepi G, Malberti F, Testa S, Mallamaci F, Zoccali C, Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risks modeling approach, J. Am. Soc. Nephrol 16 (2005) 2449–2455. [PubMed: 15944335]

[42]. Hanai K, Babazono T, Nyumura I, et al., Asymmetric dimethylarginine is closely associated with the development and progression of nephropathy in patients with type 2 diabetes, Nephrol. Dial. Transplant 24 (2009) 1884–1888. [PubMed: 19131352]

[43]. Juonala M, Viikari JS, Alfthan G, et al., Brachial artery flow-mediated dilation and asymmetrical dimethylarginine in the cardiovascular risk in young Finns study, Circulation 116 (2007) 1367–1373. [PubMed: 17724260]

[44]. Thijssen DH, Black MA, Pyke KE, et al., Assessment of flow-mediated dilation in humans: a methodological and physiological guideline, Am. J. Physiol. Heart Circ. Physiol 300 (2011) H2–12. [PubMed: 20952670]

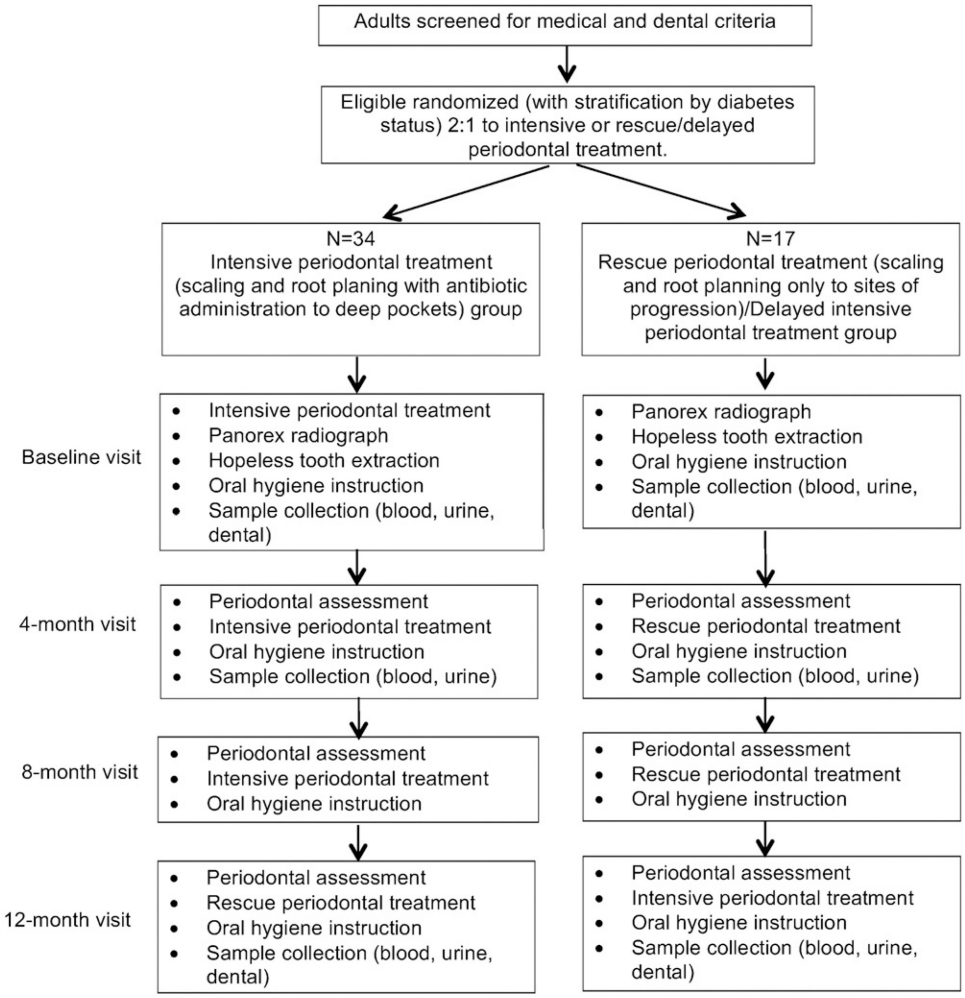

Fig. 1.
KAPD study design.

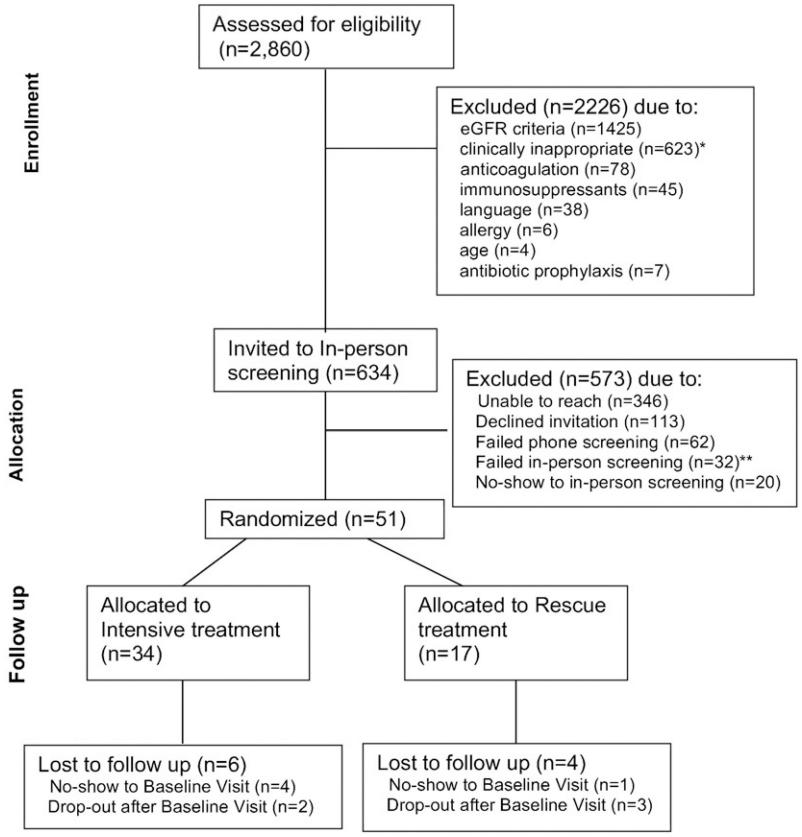

Fig. 2.

KAPD CONSORT diagram to date. eGFR: estimated glomerular filtration rate *Clinically inappropriate: deceased, n = 138; residential facility, n = 105; active drug/alcohol abuse, n = 97; homeless/no phone, n = 80; limited life expectancy, n = 73; unstable mental disorder, n = 23; transferred care, n = 20; assaultive behavior, n = 13; edentulous, n = 4; other unable to participate in study, n = 70 **In-person ineligible due to not meeting periodontal disease severity, n = 29; antibiotic prophylaxis, n = 2; dental condition requiring immediate attention n = 1

Table 1:

KAPD measures and schedules.

Measure	Study visit			
	B	4	8	12
Primary Serum				
Serum				
Creatinine	☐	☐		☐
NGAL	☐	☐		☐
ADMA	☐	☐		☐
IL-6	☐	☐		☐
C-reactive protein	☐	☐		☐
Urine				
Albumin	☐	☐		☐
Creatinine	☐	☐		☐
NGAL	☐	☐		☐
Secondary				
HbA1c	☐	☐		☐
Cotinine	☐			
Dental				
Pocket probing depth	☐	☐	☐	☐
Clinical attachment level	☐	☐	☐	☐
Bleeding on probing	☐	☐	☐	☐
Plaque index	☐	☐	☐	☐
Gingival index	☐	☐	☐	☐
Saliva	☐			☐
Subgingival plaque	☐			☐
Gingival crevicular fluid	☐			☐
Self-report				
s-TOFHLA	☐			
Sociodemographic information	☐			
Health related behaviors	☐	☐	☐	☐
Medical history	☐	☐	☐	☐
Medications	☐	☐	☐	☐
Interim medical and dental treatment		☐	☐	☐
Other				
Blood pressure	☐	☐	☐	☐
Weight	☐	☐	☐	☐

NGAL: neutrophil gelatinase-associated lipocalin.

ADMA: asymmetrical dimethylarginine.

IL-6: interleukin-6.

Table 2:

KAPD inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Medical	Age 18–64 years	Recent AKI (eGFR increase by >50% in last 6 months)
	English or Spanish language	Allergy to tetracycline or minocycline
	2 eGFR measures in last 12 months between 15 and 60 ml/min/1.73 m^2	History of infective endocarditis or heart valve repair or replacement
		Ongoing anticoagulant or immunosuppressive medication use
		Clinically inappropriate[a]
		Positive pregnancy test at screening
Dental	6 or more teeth	Presence of severe dental disease requiring immediate treatment
	Moderate or severe periodontal disease[b]	Presence of any hard or soft tissue lesion requiring further evaluation and/or treatment

eGFR: estimated glomerular filtration rate.

AKI: acute kidney injury.

[a]Clinically inappropriate: deceased, active illicit drug use, untreated psychosis, assaultive behavior, or metastatic malignancy.

[b]Moderate or severe periodontal disease as defined by CDC/AAP criteria.

Table 3:

Baseline dental measures of enrolled participants to date.

	Intervention n = 30 mean (SD)	Rescue n = 16 mean (SD)	*p*-Value[a]
Number of non-missing teeth	22.5 (5.8)	24.0 (5.0)	0.03
Number examined teeth with probing depth ≥ 4 mm	14.2 (6.8)	14.7 (6.3)	0.007
Number examined teeth with probing depth ≥ 5 mm	9.3 (6.4)	8.5 (6.8)	0.1
Number examined teeth with probing depth ≥ 6 mm	4.9 (3.9)	4.2 (4.7)	0.6
Number examined teeth with probing attachment loss ≥4 mm	12.4 (7.0)	9.4 (8.2)	0.4
Number examined teeth with probing attachment loss ≥5 mm	8.3 (6.8)	6.1 (7.5)	0.4
Number examined teeth with probing attachment loss ≥6 mm	5.5 (5.2)	3.9 (6.7)	0.3
Percent examined sites with bleeding on probing	52.2 (16.9)	58.8 (23.3)	0.004
Plaque index	1.4 (0.5)	1.5 (0.5)	0.2

[a]p-Value is Kruskal Wallis.