Diet and Hypertension Management in African Americans with Chronic Kidney Disease

NCT04084574

Document Date: 12/13/2023

Purpose of the Study

Aim 1. Identify self-perceived barriers and facilitators of DASH diet adherence among African Americans with CKD. We expect self-perceived barriers to DASH diet adherence will include economic concerns, food insecurity, convenience of unhealthy foods, personal and household member food preferences, and cultural norms. We expect the facilitators of DASH diet adherence will include perceived social support and food access.

Aim 2. Evaluate the preliminary impact of diet counseling on DASH diet adherence, 24-hour ambulatory blood pressure, and serum potassium concentration among African Americans with hypertension and CKD. We hypothesize that DASH diet counseling will increase DASH adherence score and reduce 24-hour ambulatory blood pressure without causing hyperkalemia. We hypothesize that DASH diet counseling will reduce office blood pressure without adversely affecting serum phosphorus, calcium, bicarbonate, parathyroid hormone, 25-vitamin D, creatinine, and urine albumin. We hypothesize that diet quality at 3-month follow up will be lower compared to diet quality at week 12 (immediately post-intervention), but higher compared to diet quality at baseline.

Background & Significance

Background: Compared to their White counterparts, African Americans with CKD develop CKD earlier in life, are 3 times more likely to develop kidney failure, and are 1.5 times more likely to die prematurely from CVD. Hypertension, which is also more prevalent, more severe, and less often controlled in African Americans with CKD compared to Whites, is a leading cause of CKD and CVD, and a major contributor to the racial disparity in CVD mortality. Therefore, improving hypertension in African Americans with CKD could have a profound positive impact on a significant minority health issue. Diet is a proven major disease modifier of both hypertension and CVD. Therefore, global clinical practice guidelines for the management of hypertension in CKD recommend diet modification as a “simple, inexpensive, effective” strategy to reduce blood pressure (BP) and CVD risk. Yet, there are few evidence-based diet therapies to improve hypertension and reduce CVD risk in CKD. The only diet modification that is endorsed by nephrology clinical practice guidelines to treat hypertension in CKD is sodium reduction (<2 grams/day). However, among non-CKD populations, there is strong evidence that, compared to sodium reduction, BP is lowered more effectively by the Dietary Approaches to Stop Hypertension diet (DASH) (-6/3 mm Hg compared to -2/1 mm Hg). The potential for DASH, particularly in the context of sodium reduction, to provide a greater BP benefit than sodium reduction alone, makes it an attractive treatment option for hypertension in CKD and in African Americans due to their high CVD risk burden.

DASH, which is rich in fruits, vegetables, low-fat dairy, whole grains, nuts, legumes, and is reduced in sweets and saturated fats, has been consistently shown to lower BP in adults with hypertension. In addition to its BP benefit, DASH improves glucose and lipid metabolism, and reduces estimated CVD risk. Nephrology clinical practice guidelines do not advocate for or against the use of DASH in CKD due to a lack of evidence regarding its efficacy and safety. As kidney function declines, BP becomes increasingly elevated and hypertension is more difficult to control compared to hypertension in individuals with normal kidney function. Pathologic mechanisms that contribute to hypertension in CKD include

upregulation of the renin-angiotensin-aldosterone system, overactivation of sympathetic nervous system activity, and impairment of nitric oxide induced endothelium-mediated vasodilatation. Therefore, anti-hypertensive therapies that are effective in non-CKD populations may not have the same efficacy in patients with CKD. Results from my prior studies (see my preliminary work below) which showed that DASH lowers BP in CKD, and mechanistic studies which showed that DASH counteracts factors that contribute to BP elevation CKD, and that CKD may actually be a compelling indication for DASH.

Patients with CKD have a diminished capacity to excrete minerals and electrolytes (e.g., sodium, potassium, phosphorus, and calcium) into the urine, which increases their risk for developing metabolic and acid-base disorders. As a result, physicians often advise patients with CKD to limit their consumption of foods that are high in sodium, potassium (e.g., citrus fruit, potatoes, tomatoes, and green leafy vegetables), and phosphorus (e.g., yogurt, legumes, nuts, and fish). An unintended consequence of this advice is that patients with CKD inadvertently eliminate foods from their diet that are central to "heart-healthy" dietary patterns like DASH. However, there is some evidence that DASH is safe in CKD. It has been previously demonstrated that prescribing fruit and vegetables, similar in content to DASH, to patients with severe CKD defined as an eGFR 15-29 ml/min/1.73m2 improved clinic systolic BP (SBP) (-5 mmHg, $P<0.01$), metabolic acidosis, and markers of kidney injury without negatively impacting serum potassium concentrations. Results from my pilot feeding study of DASH in CKD also suggest that DASH is safe in CKD.

Preliminary Work: Using data from the landmark DASH and DASH-Sodium trials, I have conducted secondary analyses to determine if the effect of DASH on BP is influenced by kidney function. My results demonstrate that among adults with above-normal BP and relatively normal kidney function, the efficacy of DASH is not influenced by eGFR but its effect is enhanced in the presence of low-grade albuminuria (defined as urine albumin excretion >7 mg/day). These results have direct clinical relevance for patients with CKD. Pilot feeding study: As a follow up to these studies, I evaluated the efficacy and safety of DASH in moderate CKD. I conducted a single-arm, before-after pilot feeding study that involved 11 adults with hypertension and eGFR ranging from 41.9 – 59.6 ml/min/1.72m2. All participants (10 of 11 were Black) were provided with the DASH diet (all meals, snacks and beverages) for 2 weeks. Among the 10 participants who completed the study, clinic SBP was reduced in 6 (-5 to -20 mmHg), clinic diastolic BP (DBP) was reduced in 7 (-3 to -14 mmHg), and adverse events involving hyperkalemia, hyperphosphatemia, hypercalcemia, or metabolic acidosis were not observed. Population-based study of a national Black cohort: I conducted an observational study to examine the association of DASH diet concordance with BP among 3135 participants of the Jackson Heart Study, the largest US study of CVD risk in Black Americans. I demonstrated that despite poor diet quality overall, greater DASH concordance was more strongly associated with lower BP among Blacks with CKD compared to those without CKD.

Significance: African Americans experience greater BP (-13/6 versus -6/4 mmHg) and CVD risk reductions from DASH, but are less likely to follow DASH compared to their White counterparts. There is strong evidence that counseling enhances DASH adherence among African Americans and also improves racial disparities in hypertension control rates. Factors that contribute to African Americans having a poorer diet quality compared to Whites are not fully understood but include the expense and limited availability of healthful foods, lack of knowledge about healthy dietary practices, convenience of

unhealthy food, and discordant food preferences and cultural and familial norms. Little is known about how CKD awareness influences the habitual dietary patterns of African Americans with CKD and their views about how diet contributes to CKD progression. Evidence is needed to establish the effectiveness and safety of DASH on BP in CKD. To date, no studies have explored ways to improve DASH diet adherence among African Americans with CKD. Thus, research on barriers and facilitators to following DASH diet in this patient group is essential.

Design & Procedures

Aim 1:
Study design and population – For this qualitative aim, we will recruit up to 32 African Americans ≥21 years old with a history of hypertension and moderate CKD, defined as an eGFR of 20-59 ml/min/1.73m2, who acknowledge self-awareness of their CKD diagnosis. Each participant will attend 1 focus group consisting of approximately 6-8 participants. If a participant is unable to attend one of the four focus groups, due to scheduling, they will have the opportunity for a one on one interview with a study team member by phone, Skype or Zoom, to discuss the same questions presented to the focus groups.

Protocol and data collection – All participants will fill out brief questionnaires to ascertain sociodemographic and medical histories. Focus groups will meet in a private conference room at the Duke Stedman Nutrition Center for 60-90 minutes. All interviews will be performed by an experienced qualitative interviewer using an interview guide developed by Dr. Tyson, co-mentor Fish, and the Behavioral Health and Survey Research core staff. Participants will be asked semi-structured, open-ended questions to elicit how their knowledge about CKD influences their food choices, their knowledge about the effects of diet on kidney health, their motivation and perceived ability to achieve daily targets of individual DASH diet components, and self-perceived barriers and facilitators of following DASH. All interviews will be audio-recorded, transcribed verbatim, and checked for accuracy. We may conduct individual semi-structured interviews in addition to focus groups, if needed, to capture perspectives presumed to be missing from the focus group discussion. Using these two different methods to collect qualitative data will ensure that we achieve thematic saturation. Results from this phase will be used to inform the design of the 12-week DASH diet counseling intervention that will be tested in Phase 2.

Aim 2:
Study design and population – We will recruit 50 African Americans ≥21 years old with a history of hypertension and moderate-to-severe CKD defined as an eGFR of 20-59 ml/min/1.73m2. Participants will be randomized in 1:1 fashion to a standard-of-care control arm or an intervention arm.

Study protocol
Control arm: Participants in the control arm will meet individually with the study dietitian for a single 30-minute diet counseling session that will occur face-to-face or via videoconference. They will be advised to limit sodium intake to less than 2.3 grams/day per 2020 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guideline for nutrition in CKD. They will be given educational handouts and tip sheets on how to reduce dietary sodium. Because DASH is not included in current CKD

nutrition guidelines and is not standard-of-care in CKD, participants in the control arm will not be provided with information about the DASH diet. Participants will be permitted to bring one household member/health advocate with them to their counseling session since engagement and social support during nutritional counseling is associated with improved diet adherence.

Intervention arm: Similar to the control arm, participants in the intervention arm will also meet individually with the study dietitian for a single 30-minute counseling session to limit daily sodium intake to less than 2.3 grams/day. However, intervention arm participants will additionally attend 12 weekly dietitian-led group counseling sessions lasting approximately 60-90 minutes. Group counseling will occur in-person and/or via videoconference and will aim to increase participants' adherence to the DASH dietary pattern. Participants will be permitted to bring one household member/health advocate with them to their counseling sessions since engagement and social support during nutritional counseling is associated with improved diet adherence.

All participants will be asked to continue their same anti-hypertensive medications (i.e., no dose changes) and maintain their usual level of physical activity during the 3-month study period. All participants will also have the option to consent to an additional blood sample to be collected, stored and used for future research.

Data collection – A timeline for data collection visits and schedule of assessments are shown in Table 1. Questionnaires will be used to ascertain information about socio-demographics, medical histories, medications, physical activity, self-efficacy, perceived social support, food environment, sleep and health-related quality of life.

- Physical measures of height and weight will be obtained using standard methods.
- Venipuncture will be performed to obtain blood samples for laboratory testing to determine participants' study eligibility and metabolic/physiologic responses to DASH.
- These laboratory studies will include a basic metabolic panel, calcium, albumin, phosphorus, hemoglobin A1c, fructosamine and lipids.
- 24-hour urine samples will be collected to objectively assess diet adherence with DASH and to track physiologic response to diet modification.
- Urine biomarkers will include sodium, potassium, magnesium, calcium, phosphorus, urea, creatinine, albumin. All biospecimens will be processed by a CLIA-certified laboratory (LabCorp, Burlington, NC).
- Office BP will be measured using a validated, semi-automated oscillometric BP device and 24-hour ambulatory BP monitoring will be performed using a validated automated device following guideline standards.
- Diet will be assessed using self-administered 24-hour dietary recalls using the Automated Self-Administered 24-Hour (ASA24®) Dietary Assessment Tool.
- Stool specimens will be obtained using a standardized protocol and processed by the Duke Microbiome Center.
- Post-intervention semi-structured interviews will be performed among active arm participants to identify self-perceived barriers and facilitators of diet adherence, impact of diet modification on quality of life, and suggestions about how to improve the diet intervention.

Post-study opportunity for participants randomized to the control group:
Study participants who were randomized to the control group will have the opportunity to attend 6 weekly virtual diet information sessions after they complete final data collection visits and exit the study. Only participants whose schedules are compatible with course offerings by the dietitian will be able to attend. Diet information will align with national professional kidney organization recommendations. No research or monitoring data will be collected on participants who attend the 6-week session block. Invitations to participant in the post-study diet sessions will be mailed and/or emailed to former participants. Participants may also be contacted by phone by study staff and invited to participate.

Opportunity for participants who were screening for Cohort 5 during study cancellation:
We will provide an opportunity for study participants who were in the midst of screening for Cohort 5 to attend the diet counseling sessions that they otherwise would have received had we not ended the study. This will involve a one-on-one virtual diet session and 6 virtual diet group sessions led by the study dietitian, which is the same amount of access to the study dietitian that the control group was offered during the study. Participants will complete an in-center screening visit, per protocol, to confirm that it is safe to attend counseling sessions. Those who pass screening, thereby demonstrating that their blood pressure and labs meet original inclusion criteria, will be invited to participate in diet sessions only. Only participants whose schedules are compatible with course offerings by the dietitian will be able to attend. Diet information provided during the sessions will align with national professional kidney organization recommendations. Other than data collected during the screening visit, no research or monitoring data will be collected on participants who attend the 6-week session block. Because this activity is not a part of the research and does not involve an intervention, study participants will not be reconsented.

Selection of Subjects

Aim 1 Inclusion Criteria:

- Black race (self-identified)
- ≥21 years old
- CKD defined as an eGFR of 20-59 ml/min/1.73m2
- acknowledges self-awareness of CKD diagnosis
- Exclusion Criteria
- History of kidney transplant
- Lack of English language proficiency

Aim 2 Inclusion Criteria:

- Black race (self-identified)
- ≥21 years old
- CKD defined as an eGFR of 20-59 ml/min/1.73m2
- SBP ≥100 mm Hg
- Stable kidney function

- Videoconference capabilities (access to mobile phone, laptop, desktop or tablet with working camera and internet connectivity)

Exclusion Criteria

- History of kidney transplant
- Receiving chronic dialysis
- Pregnant, lactating, or planning to become pregnant in 9 months
- Risk factors for hyperkalemia
- Screening serum potassium >5.0 mg/dl
- Screening serum bicarbonate <20 mg/dl
- History of hyperkalemia in the preceding 6 months defined as serum potassium greater than 5.0 mg/dl
- Use of oral potassium binders
- Dual therapy with an ACEI and an ARB
- Type 1 diabetes mellitus
- Type 2 diabetes with increased risk for glycemic event
- Hemoglobin A1C >10
- Hospitalization for glycemic event within the preceding 12 months
- If prescribed insulin or insulin secretagogue and unable to obtain permission from diabetes provider to participate in the study
- Change in anti-hypertensive medications within prior 4 weeks
- Hospitalization for hypertensive emergency in the preceding 6 months
- Hospitalization for psychiatric event in preceding 6 months
- Lack of English language proficiency
- Cardiovascular event within the preceding 12 months
- Excess alcohol use (>14 servings/week)
- Active malignancy other than prostate cancer and non-melanomatous skin cancer
- Inability to follow the study diet
- Special dietary requirements or restrictions other than vegetarianism (e.g., vegan)
- Resident of long-term care facility
- Household member of active study participant
- Participating in another clinical trial that will interfere with study activities or confound study outcomes

Subject Recruitment and Compensation

This study will use tools available in Maestro Care, such as DEDUCE (Duke Enterprise Data Unified Content Explorer) and Slicer/Dicer search tools, to help identify and recruit potential participants before consent is signed. We will also screen the schedules of clinics that are attended by our target population in high volume (e.g., nephrology, cardiology, hypertension clinic). Only key personnel who are delegated the task of patient identification/recruitment will have access to this information in Maestro Care. Prospective participants will be referred to the study by the following means:

Face-to-face contact during clinic visits: With the permission of and in coordination with the patient's healthcare provider, trained study personnel will be introduced to patients by their provider during their scheduled clinic appointment. The research personnel will inform patients about the study and invite them to participate.

Direct contact: This study will use a Maestro Care MyChart recruitment invitation to help identify potential participants pre-consent. Potential subjects are identified via a report generated within Maestro Care by the DOCR Maestro Care Analyst team. A recruitment invitation will be sent by a DOCR analyst to potential subjects via MyChart. The patient will indicate if they are interested or not interested and the study coordinator will be sent an Inbasket message (Maestro Care internal message) indicating the response. Only key personnel who are delegated the task of patient identification/recruitment will have access to the Inbasket messages. Only patients who express interest will be contacted by key personnel, who will then follow the recruitment process approved by the IRB for this study. Patients who do not have an active MyChart account will be mailed or emailed an IRB-approved study introduction letter inviting them to complete an online screening survey to determine their study eligibility. Emails will be sent secure. We will contact patients by phone after at least 1 week of mailing the letter to gauge their interest in participating. Patients will not be contacted by phone more than 3 times during the recruitment process.

Direct clinican referral: Patients' health care provider may introduce the study and refer them to participate.

Direct-to-participant marketing: Participants may learn about the study on the Duke Clinical Trials Directory (DukeHealth.org), ClinicalTrials.gov, an IRB-approved study website, ResearchMatch (a nonprofit program funded by the National Institutes of Health), and on the Discover Duke Research Facebook (https://www.facebook.com/DiscoverDukeResearch/?ref=py_c) and Instagram (https://www.instagram.com/discoverdukeresearch/) pages.

During the first phase (Aim 1) thirty-two eligible participants will be recruited and enrolled to participate in one of four scheduled focus groups. Aim 1 participants will be mailed a check for $50 after they have completed their focus group to compensate for travel and/or lost wages.

During the second phase (Aim 2) fifty participants will be recruited, enrolled and randomized 1:1 to either the Standard of Care (Control) Group or the Intervention Group. Participants in both groups will be compensated up to a total of $250 for travel, lost wages, and time. ClinCards will be given to each participant and payments for each of the 4 data collection visits will be uploaded after the assessments that are assigned to each respective visit are completed. They will receive: $50 for completing all baseline assessments, $50 for completing all 4 week assessments, $100 for completing all 12 week assessments, and $50 for completing all 24 week assessments. Payments will be prorated for completing questionnaires, biospecimens, BP measurements, and dietary recalls at each visit.

Participants who consent for Aim 2 will have the option of sharing their experiences and thoughts about participating in research with the Duke Research Equity and Diversity Initiative (READI) project. The READI project aims to better understand and improve participants’ experiences in research studies.

Participants will indicate on the consent form whether they agree to share their contact information (name and email address) with the READI project, or not. If they do, they will be invited to share the information on their experience through surveys.

Participants enrolled and randomized in Aim 2 will have the option to choose to have additional blood samples collected and stored for future research. This option requires participants to sign a separate consent form that provides details about the storage and potential future use. The additional sample will be collected at the same time other blood draws are conducted for the main study. No additional visit or venipuncture will be required and no additional compensation will be provided for the optional collection.

Risk/Benefit Assessment

Potential risks: (Phase 2 participants only)

- Electrolyte abnormalities
- Hyperkalemia: the DASH diet is rich in potassium. Urinary excretion of potassium is diminished as kidney function worsens. If severe, hyperkalemia can result in muscle weakness and paralysis, cardiac conduction abnormalities, cardiac arrhythmias, metabolic acidosis and death.
- Hyperphosphatemia: the dairy and protein content of the DASH diet makes it a rich source of phosphorus. Urinary excretion of phosphorus is reduced in advanced kidney disease. Although unlikely, sudden, severe hyperphosphatemia, can cause hypocalcemia and result in muscle paralysis or calcium-phosphate deposition into soft tissue.
- Hypoglycemia: Although the DASH diet is not a low-carbohydrate diet (approximately 55% of daily calories from carbohydrates), individuals with type 2 diabetes mellitus who are prescribe insulin or insulin secretagogues will be at risk for developing hypoglycemia if their typical daily intake of carbohydrates is higher than the DASH diet. Hypoglycemia can cause tremor, diaphoresis, confusion, tachycardia, hunger and nausea, fatigue, headache, blurred vision, and irritability. If severe and left untreated hypoglycemia can lead to seizure, loss of consciousness, and death.
- Complications from venipuncture: Venipunctures may cause some momentary discomfort and/or bruising at the site of needle entry. Infection, excess bleeding, or clotting are also possible, although unlikely. Occasionally, blood drawing can cause dizziness, lightheadedness, nausea and/or fainting.
- Food allergy and lactose intolerance: Participants may be exposed to new foods, creating the possibility for a food allergy to be discovered resulting in an allergic reaction. In addition, they will be provided a diet that is rich in dairy, possibly leading to symptoms of lactose intolerance.
- Loss of confidentiality (Phase 1 and Phase 2 participants): Privacy in the context of this study includes confidentiality of data and personal information and in handling and reporting of data.
- Risks of serious electrolyte abnormalities will be minimized by excluding participants who have elevated serum potassium concentrations at baseline and who are at risk for developing hyperkalemia. Furthermore, surveillance labs will be drawn at pre-determined intervals during the study to assess for changes in key CKD-relevant electrolytes and minerals and participants

will be counseled to modify their diet, if necessary, to correct the abnormality, or withdrawn from the study at the PI's discretion for safety. Risk of hypoglycemia will be minimized by excluding participants with history of being hospitalized for a glycemic event 12 months preceding study enrollment and with A1C >10. In addition, participants who are on insulin and insulin secretagogues will be required to have the permission of their diabetes provider to participate in the study and their diabetes provider will agree to adjust their medications, if indicated, during the study. Risk of loss of confidentiality will be minimized by ensuring the physical privacy of participants during face-to-face interviews, discussing expectations of confidentiality with all group participants, and storing research documents in a secured area accessible only to the study staff. All staff will be trained regarding these procedures.

Potential benefits: (Phase 2 participants only)

- Improved blood pressure
- Reduced CVD risk
- Improved blood glucose
- Improved lipids
- Contribute to health-related knowledge that may serve to benefit patients with CKD in the future (Phase 1 and Phase 2 participants)
- Alternatives to participating: (Phase 2 participants only) - pharmacologic and non-pharmacologic strategies to control hypertension and CKD as recommended by patients' healthcare provider.

Importance of the knowledge expected to result from the research: Phase 1 - knowledge generated from focus groups will inform the design of the culturally-sensitive and disease-relevant diet counseling intervention that will be delivered in Phase 2. Phase 2 - knowledge will determine the preliminary effectiveness and safety of DASH diet counseling to lower BP among Blacks with CKD.

Data Analysis & Statistical Considerations

Phase 1 analytic strategy

We anticipate that participants will be accrued within a 12 months period. We will use a 5 stage approach to conduct thematic analysis (familiarization; identifying a thematic framework; indexing; charting & mapping, and interpretation). Experienced qualitative researchers from the Duke Behavioral Health Research Core will perform the analysis. Familiarization with the data will involve the entire research team reviewing 2-3 transcripts to identify initial coding themes. The identified themes will be used as the initial coding framework to conduct line by line coding of a single transcript. The team will meet to discuss the transcript and modify the initial framework. Next, two experienced qualitative researchers will conduct line by line coding of remaining transcripts. Coding will include memos for each transcript to annotated coders questions, decision about the data, and reflections on analysis. Each coder will also create an overview memo to collect observations that cut across individual transcripts during the coding process. After coding is completed, the team will meet to discuss themes, sort codes, and restructure the initial framework as similarities and differences are identified. In the final stage, the team will identify major themes and associated quotes to summarize the results. Methods such as

regular debriefing and providing rich thick description in memos will be used to enhance rigor and trustworthiness of study findings. Data will be analyzed using Atlas.ti (version 7.5).

Phase 2a analytic strategy

We anticipate that participants will be accrued within a 18 month period at a rate of 3 participants per month. To determine the feasibility of conducting our intervention in a larger randomized controlled trial, we will evaluate rates of study enrollment, group attendance, completed data collection, and study retention. We will also assess reasons for study refusal and withdrawal. We will consider the study feasible if we are able to recruit 50 participants in 18 months. To determine acceptability, we will ask participants how useful the intervention was (1="Not at all useful" to 5="Extremely useful"), whether the intervention will change their diet (1="Will not change at all" to 5="Will change a lot"), and whether they would recommend the program to a friend (1="Definitely would not recommend" to 5="Definitely would recommend"). For the intervention to be deemed acceptable, 75% of participants in the intervention group would have to rate each item a "4" or a "5."

Phase 2b analytic strategy

To evaluate preliminary efficacy of our counseling intervention on DASH adherence, BP, and potassium, we will repeat 24-hour diet recalls, 24-hour urine biomarker studies, office BP, 24-hour ABP, and clinical laboratory studies for all study participants at weeks 12 (post-intervention; primary endpoint) and 24 (after a 3-month post-study observation period; exploratory endpoint). We anticipate that active arm participants will exhibit greater improvement in DASH adherence and a larger reduction in 24-hour mean SBP. Initial summary statistics and graphical displays will be used to make reasonable outcome distribution assumptions. Using an intention to treat, primary analyses to compare the amount of change over time and trajectories of change between the two study arms in DASH diet score, 24-hour mean SBP, and serum potassium will use generalized linear mixed models, with a random effect to capture longitudinal within-person correlation. The primary model for BP outcomes will include study arm, time point, and their interactions, consistent with the randomized trial. Subsequently, a secondary model will be refit to adjust for age, gender, race baseline daily sodium intake, and time-specific values of eGFR, weight, and hypertension medication indicator. Exploratory outcomes in office SBP and DBP, 24-hour DBP, 24-hour urine biomarkers of diet adherence (potassium, phosphorus, urea, and sodium), and additional CKD-relevant metabolic markers (serum phosphorus and bicarbonate) will be assessed using the same analytic strategy. Our analytic approach can be used with any distribution within the exponential family (e.g., normal, binomial, Poisson, and skewed distributions such as gamma and lognormal). The decision on which is most appropriate will be made using initial summary statistics and graphs. The exponential family is broad enough that further transformations of the data are not expected to be necessary, but if so, we will use historically-common transformations to approximate normality. The proportion of participants who do and do not meet safety thresholds (serum potassium >5.2 mg/dl per testing lab standards, phosphorus >5.5 mg/dl, bicarbonate <18 mmol/L) in the two study arms will be compared using the same longitudinal generalized linear mixed model approach, assuming the Binomial distribution.

Unlike a large clinical trial, our pilot study will not have statistical power to establish the effectiveness and safety of DASH in this population. However, this initial pilot study will generate critical evidence for estimating effect sizes and showing feasibility of the intervention, that will guide future work. Power:

Our power estimate is based on the primary aim comparing treatment arms on the SBP measure. Assuming a 20% attrition rate of 5 per group and using two-sided tests at a type I error rate of 5%, a final sample size of 20 per group will give us 80% power to detect a 7.7 mmHg difference in the change in SBP at 12 weeks between groups, assuming a within-person correlation of 0.7 over time and a standard deviation of SBP of 11 mmHg. A between-group difference of 11.4 and 7.8 mmHg were observed in prior DASH feeding and counseling intervention studies. To assess the sensitivity of the results to any missingness in the data, we will use multiple imputation to create complete cases while incorporating the uncertainty in doing so in the assessment of model parameters. The SAS/STAT software, version 15.1 for Windows and R packages (version 3.6.1) will be used for the data analyses, after extraction from the research database REDCap (Research Electronic Data Capture).

Phase 2c: For this qualitative aim, self-reported barriers and facilitators to DASH diet adherence among active arm participants will be described. Interview transcripts will be analyzed using framework analysis. A thematic analysis approach will be used to allow new concepts to emerge inductively from the data.

Data & Safety Monitoring

Safety monitoring:

Hyperkalemia: Hyperkalemia is the most serious potential risk that CKD patients who follow the DASH diet may experience. Therefore, we plan to actively monitor serum potassium concentrations during the intervention and intensify monitoring during periods that elevations in potassium, if they occur, would most likely be observed. When and how frequently we plan to measure serum potassium has been determined by:

- when participants will be counseled about potassium-rich and potassium-poor foods by the dietitian (i.e., week 2-3);
- knowledge about timing of steady-state concentrations of potassium following increased oral intake; and
- lessons learned from our DASH diet pilot feeding study in which we observe trends in serum potassium among patients with CKD stages 3a and 3b who were given the DASH diet (i.e., Black adults with CKD). Participants in the feeding study had slightly lower risk for hyperkalemia due to their higher eGFR compared to the target population (CKD stages 3b and 4) being recruited for the current study.

As outlined in our proposal, serum potassium will be measured at the following scheduled intervals for participants who are randomized to the DASH diet counseling intervention: weeks 0, 2, 4, 8, and 12. Additionally, we plan to perform reflex laboratory testing contingent on the results from scheduled testing.

Blood pressure is a primary outcome for the study and will be measured during scheduled data collection visits. The study PI will be alerted during the study visit about participants with symptomatic severe hypertension or hypotension to make timely decisions about medical referral.

Hypoglycemia: Although DASH is not a low-carbohydrate diet, participants with Type 2 Diabetes Mellitus (T2DM) may be at risk for developing hypoglycemia if the carbohydrate content of DASH is lower than their typical daily consumption and they are prescribed insulin or insulin secretagogues. Safety oversight for study procedures involving patients with T2DM will be provided by Dr. Alexopolous, who is a Duke board-certified endocrinologist who specializes in caring for patients with diabetes. Investigators will take the following precautions to minimize risks of hypoglycemia and enhance the safe participation of patients with T2DM in the study:

Agreement of participants' diabetes provider (DP) to manage blood glucose (BG)
Investigators do not assume responsibility for clinical care of the participants' diabetes. Potential participants with T2DM who are prescribed insulin or an insulin secretagogue will only be allowed to participate in the study if their DP (i.e., primary care provider or endocrinology provider) approves of their participation and agrees to manage their diabetes medications during the study (see "Diabetes Provider Opt-in Contact Protocol"). Participants will be advised to maintain follow up appointments with their DP and to seek sooner follow-up if indicated for abnormal glucose values.

Blood glucose self-monitoring
It is common practice for individuals with T2DM who are prescribed insulin to be advised by their DP to monitor their BG concentrations several times per day (e.g., at least once daily for basal insulin users, approximately 3-4 times daily for basal-bolus insulin users). Participants will be advised to continue to follow their providers' advice regarding how often they monitor their BG. Since the study population may be at heightened risk of hypoglycemia due to the presence of CKD, the study team will provide each participant with diabetes with a handout based on ADA material that reviews hypoglycemia precautions (see "Hypoglycemia (Low blood sugar)" handout) and encourage them to contact their provider to report hypoglycemia so medications may be adjusted if indicated. As a precaution, hypoglycemia will be defined as BG <80 mg/dl, instead of <70 mg/dl, given this is a higher risk population.

Assessment of baseline dietary pattern
All study participants who meet inclusion criteria will be asked to complete 2-3 dietary recalls at baseline. We will determine typical daily carbohydrate consumption for all participants with T2DM who are prescribed insulin or insulin secretagogues and are randomized to the intervention arm. We will communicate participants' typical daily carbohydrate consumption to their DPs to make them are aware of how their participant's current carbohydrate amount compares to the DASH diet. This information can be used at the discretion of the DP to help triage when the patient should be seen to decide on appropriate follow up.

Study withdrawal
Individuals who require hospital admission for a glycemic event during the study period will be withdrawn from the study.