Title
Dietary phosphorus intake among a diverse cohort of end-stage renal disease hemodialysis patients.

Author
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Publication Date
2020

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA,

IRVINE

Dietary phosphorus intake among a diverse cohort of end-stage renal disease hemodialysis patients.

DISSERTATION

submitted in partial satisfaction of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in Public Health

by

Amanda Brown

Dissertation Committee:

Professor Kamyar Kalantar-Zadeh, Chair

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2020

DEDICATION

To

my children,

thank you for inspiring me every day.

To

my parents,

thank you for all your love.

And to my husband,

thank you for all your support.

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ACKNOWLEDGEMENTS

I would like to thank my primary mentor, Dr. Kalantar, for working diligently to ensure my success during the PhD program and beyond. Your work ethic and zest for innovation are truly admirable, and I am grateful to have worked with your world-renowned research team and colleagues.

I would like to thank Dr. Annie Ro, for being one of the best professors I've had in all my years of education. I genuinely looked forward to attending all your classes.

I would also like to thank Dr. Connie Rhee, for providing positive, and supportive guidance over the years.

To Dr. Oladele Ogunseitan, thank you for inspiring me to pursue my goal of changing the world. Your steadfast optimism encouraged me to join the UCI Program in Public Health, and for that I am grateful.

Many thanks to all my classmates for the numerous study sessions, thoughtful conversations, and comradery. Special thanks to Tamara for caring for my children.

I would like to acknowledge my sincere appreciation to everyone who helped me apply for my F31 grant and carry out my research study, including Dr. Keith Norris, Dr. Elani Streja, Tracy, Kristine, Amy, Kimberly, Alejandra, and Dr. Yoko Narasaki.

I would also like to thank everyone who provided fellowships which allowed me to dedicate time to completing original research for my dissertation, including the National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, Network of Minority Research Investigators, American Society of Nephrology, and the Program in Public Health. Special thanks to the Program in Public Health for your support during my maternity leaves.

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Ph.D., Public Health, University of California, Irvine (2020)
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Principal Investigator

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TEACHING EXPERIENCE

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Director, Campus Communications

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Health Science Graduate Student Representative

- Support public health, nursing, and pharmacology students through representation at graduate student governance council meetings

Graduate Student Parent Advisory Board Member

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UC Irvine, Department of Population Health & Disease Prevention 2019-Present

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PROFESSIONAL EXPERIENCE

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PEER-REVIEWED PUBLICATIONS

Brown-Tortorici, A. R., Naderi, N., Tang, Y., Park, C., You, A. S., Norris, K. C., ... & Rhee, C. M. (2020). Serum albumin is incrementally associated with increased mortality across varying levels of kidney function. *Nutrition*, 110818.

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Kim, T., Rhee, C.M., Streja, E., Soohoo, M., Obi, Y., Chou, J.A., **Tortorici, A.R.**, Ravel, V.A., Kovesdy, C.P. and Kalantar-Zadeh, K. (2017). Racial and ethnic differences in mortality associated with serum potassium in a large hemodialysis cohort. *American Journal of Nephrology*, *45*(6), pp.509-521.

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Kalantar-Zadeh K, Moore L, **Tortorici A**, Chou J, St. Jules D, Aoun A, Rojas-Bautista V, Tschida A, Rhee C, Shah A, Crowley S, Vassalotti J, Kovesdy C. (2016). North American experience with low protein diet for non-dialysis-dependent chronic kidney disease. *BMC Nephrology. 17:90* doi: 10.1186/s12882-016-0304-9.

Kalantar-Zadeh K, **Tortorici AR**, Chen JL, Kamgar M, Lau WL, Moradi H, Rhee CM, Streja E, Kovesdy CP. (2015). Dietary restrictions in dialysis patients: is there anything left to eat? *Semin Dial.* 28(2):159-68. doi: 10.1111/sdi.12348.

SELECTED POSTER PRESENTATIONS

Tortorici A, Naderi N, Tang Y, Park C, You A, Norris K, Obi Y, Streja E, Kalantar-Zadeh K, Rhee C. Serum Albumin and All-Cause Mortality Across Varying Levels of Kidney Function. Poster presentation at American Society of Nephrology 2019 Kidney Week Annual Meeting.

Tortorici A, Kalantar-Zadeh K, Streja E, Juarez K, Novoa A, Nakata T, You A, Rhee C. Dietary Phosphorus & Protein Intake In A Diverse Cohort Of Hemodialysis Patients. Poster presentation at American Society of Nephrology 2018 Kidney Week Annual Meeting.

Tortorici A, Kalantar-Zadeh K. Qualitative Analysis of Diet and Adherence in Veteran End-Stage Renal Disease Hemodialysis Patients. Poster presentation at 2017 NIDDK Network of Minority Health Research Investigators West Regional Meeting.

Tortorici AR, Streja E, Rhee C, Soohoo M, Lau WL, Obi Y, Sim J, Gillen D, Norris KC, Kovesdy C, Kalantar-Zadeh K. Both Low and Very High Serum Phosphorous Levels Prior to Transition to Dialysis are Associated with Early Dialysis Hospitalization in US Veterans: A Transition of Care in CKD Study. Poster presentation at American Society of Nephrology 2016 Kidney Week Annual Meeting.

Tortorici AR. Calcium intake and risk of eating disorder in male and female high school athletes. April 2016. Presentation at 2016 Sports, Cardiovascular, and Wellness Nutrition (SCAN) practice group annual symposium.

Tortorici AR, Obi Y, Soohoo M, Rhee C, Streja E, Jing J, Saran R, Robinson BM, Li Y, Nguyen DV, Norris KC, Kovesdy CP, and Kalantar-Zadeh K. November 2015. Serum phosphorous levels prior to transition to dialysis and early dialysis mortality among us veterans: A transition of care in CKD study. Poster presentation at American Society of Nephrology (ASN) Kidney Week 2015 Annual Meeting.

Brown, A., Kayed, R., Glabe, C. (2005, February). Characterization, specificity, and affinity evaluation of conformation specific antibodies against different amyloid species, using ELISA, Dot blot, and Western. Poster presentation at American Association for the Advancement of Science Annual Meeting; Washington DC.

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- **NIH F31 Fellowship Recipient Panel,** University of California, Irvine, March 2019
- **Plant-Based Diets & Chronic Kidney Disease,** University of California, Irvine Medical Center, January 2019
- **Dietary Assessment Methods in CKD Patients,** University of California, Irvine Medical Center, January 2018
- **NIH F31 Ruth L. Kirschstein National Research Service Award Workshop**, University of California, Irvine, Department of Psychology and Social Behavior, February 2017
- **Sources of Dietary Phosphorus and Management of Dietary Phosphorus in ESRD Hemodialysis Patients**, University of California, Irvine Medical Center, March 2016.
- **Low protein diet to help control disease progression and to attenuate protein energy wasting in CKD patients**, Veterans Affairs Long Beach Health Care System, June 2014
- **Fueling the Plant-Based Athlete**, Inland District Dietetic Association, Rancho Cucamonga, May 2014
- **Performance Nutrition,** Kaiser Permanente Sports Medicine Practice Group Continuing Education Series, Orange, CA, Nov 2013
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Loyola University African, Latino, Asian, & Native American Scholar (2000-2004)

ABSTRACT OF THE DISSERTATION

Dietary phosphorus intake among a diverse cohort of end-stage renal disease hemodialysis patients.

By

Amanda Brown

Program in Public Health

University of California, Irvine 2020

Kamyar Kalantar-Zadeh, Chair

Background: Hyperphosphatemia is a known predictor of mortality in hemodialysis patients. Disruption of serum phosphorus levels have been related to subsequent disruption of parathyroid hormone and calcium homeostasis. These disruptions in mineral and hormone balance may lead to left ventricular fibrosis and hypertrophy, vascular calcification, and eventually sudden cardiac death. Hemodialysis often does not sufficiently remove enough phosphorus to reach recommended concentrations of serum phosphorus, making hyperphosphatemia common among hemodialysis patients.

Current renal dietary guidelines recommend for patients to consume a low phosphorus diet in order to reduce the risk of hyperphosphatemia. However, there are few studies to support this dietary practice. In the studies that exist, there have been conflicting reports concerning the outcomes of dietary phosphorus restriction. As lowering dietary phosphorus has the potential to concomitantly reduce intake of heart-healthy macro- and micronutrients, and increase risk of protein energy wasting, there is discussion for liberalization of diet with greater emphasis on serum phosphorus management with a focused reduction in inorganic phosphorus additives and phosphorus binder medications. This study utilized hemodialysis patients participating in the Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease (MADRAD) study.

Objectives: In this dissertation, I measured the association between absoulute dietary phosphorus intake, phosphorus/1000 kcal, and phosphorus-to-protein ratio and mortality in MADRAD study patients (Chapter 2); analyzed data from 3-day diet records collected from MADRAD study patients to gain insight into dietary phosphorus intakes and related dialysis patient clinical and sociodemographic characteristics (Chapter 3); and investigated dialysis patients' perceptions of the renal diet, behaviors and attitudes of renal clinicians, and how they related to dietary adherence (Chapter 4).

Methods: Study participants are enrolled in the Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease Study. In Chapter 2, primary analyses included examining the association between measures of dietary phosphorus intake (absolute intake, phosphorus/1000 kcal, and phosphorus-to-protein ratio), categorized into tertiles and quartiles, and all-cause mortality. In Chapter 3, primary analyses involved conducting logistic regression analyses to examine the association of sociodemographic, comorbidity, dialysis treatment, health insurance, and dietary intake characteristics with likelihood of above median dietary intakes of phosphorus-to-total-protein ratio, phosphorus-to-plant-protein ratio, phosphorus/1000 kcal, and plant-protein-to-total-protein ratio, respectively. In Chapter 4, a semi-structured interview was conducted with two male hemodialysis patients and their renal clinicians were also observed.

Results: In Chapter 2, the lowest intakes of absolute dietary phosphorus intake, phosphorus/1000 kcal, and phosphorus-to-protein ratio were associated with mortality in unadjusted models and various models of expanded levels of adjustment. In expanded case-mix spline analyses that examined the association of daily dietary phosphorus as a continuous variable and mortality risk, there was a trend that daily dietary phosphorus intake in the lowest tertile was associated with higher death risk. In Chapter 3, I found that predictors of dietary phosphorus and protein intake

included Black race, female sex, older age, and being single. In Chapter 4, I found that factors associated with patient dietary adherence included social support, self-efficacy, self-discipline, barriers, and cultural food norms. Renal clinicians were perceived as being supportive and encouraging in setting dietary goals and being accountable.

Conclusion: The finding that lower dietary phosphorus intake in dialysis patients is associated with greater death risk contradicts current recommendations for dialysis patients to eat a low phosphorus diet. Intake of dietary phosphorus is related to many modifiable and non-modifiable patient characteristics, and dietary recommendations may need to be liberalized with a focus on more enjoyable unprocessed whole foods and reductions in added phosphorus.

Chapter 1: Introduction

Dietary Phosphorus, Adherence, and Public Health Burden in Hemodialysis Patients

Regulation of phosphorus intake through food is of particular importance due to evidence that hyperphosphatemia is associated with an increased risk of mortality in end-stage renal disease (ESRD) hemodialysis patients.[1-3] The *Kidney Disease Outcome Quality Initiative* (KDOQI) guidelines define hyperphosphatemia in dialysis patients as having serum phosphorus > 5.5 mg/dL.[4,5] Hemodialysis patients are advised to have a maximum of up to 800-1000 mg of phosphorus per day to prevent hyperphosphatemia[6], as compared to the Recommended Dietary Allowance for phosphorus in healthy adults, which is 700 mg/day with an Upper Limit of 4000 mg/day.[7] Even within the general population, elevated levels of dietary phosphorus intake >1400 mg/day have been associated with increased risk of all-cause mortality.[8]

Hyperphosphatemia may lead to increased mortality by increasing additional hormonal and mineral imbalances associated with cardiovascular disease. Disruption of serum phosphorus levels have been related to subsequent disruption of parathyroid hormone and calcium homeostasis.[9] These disruptions in mineral and hormone balance may lead to left ventricular fibrosis and hypertrophy[10,11], vascular calcification[12], and eventually sudden cardiac death.[13,14] Cardiovascular disease has been the leading cause of death in dialysis patients, comprising over 40% of all deaths in this population.[15]

Most foods contain some amount of phosphorus, however, it is naturally abundant in foods that are good sources of protein.[16] The bioavailability of phosphorus, the fraction of ingested phosphorus that is absorbed through the intestines, ranges from 20% to nearly 100% and depends on several variables. These factors include the source of phosphorus, i.e., organic plant protein vs. organic animal protein vs. inorganic or added phosphorus and the influence of such factors as vitamin D, which may modify the amount of phosphorus absorbed via the intestines.[17]

The bioavailability of organic phosphorus from animal-based proteins is moderate, with 40 to 60% of the phosphorus being absorbed in the intestines.[18] While in the intestines, organic phosphorus is broken down into organic PO_4 and absorbed into the bloodstream. Sources of phosphorus in animal-based protein include chicken, fish, seafood, dairy, and red meat.

Plant proteins include nuts, legumes, seeds, and grains. Whereas the phosphorus in animal protein is readily degraded and absorbed, the phosphorus in plant proteins is mostly found in the less accessible form of phytate or phytic acid. Humans do not express the enzyme phytase to effectively digest phytates, therefore leading to lower rates of absorption in plant proteins. Consequently, phosphorus bioavailability from plants is relatively low, with approximately 20-40% absorption.[19]

Since there is much greater bioavailability of inorganic phosphorus, this type of dietary phosphorus may have a larger influence on hyperphosphatemia in dialysis patients than an equal amount of dietary organic phosphorus.[20] Inorganic phosphorus is not naturally found in foods, but is usually found as an additive in processed foods. It serves many purposes including extending shelf life, improving the color of food, enhancing flavor, and helps to retain moisture.[19,21] It is found in a variety of food products including colas, cereals, processed cheeses, instant products, and deli meats.[22] As opposed to organic phosphorus, inorganic phosphorus is not bound to protein; therefore, it is easily and readily absorbed through the intestines. It has been estimated that 90-100% of inorganic phosphorus additives are absorbed and they contribute up to 1000 mg per day of daily dietary phosphorus.[23,24]

Even though current guidelines recommend a low phosphorus diet, there is conflicting evidence surrounding a definitive association between dietary phosphorus and mortality. A study by Lynch et al. found that a prescription of low dietary phosphorus was not associated with a survival benefit among hemodialysis patients, with results suggesting the low phosphorus diet may potentially be harmful.[25] In another study following over 30,000 hemodialysis patients, compared to patients with a 6-month increase in serum phosphorus and dietary protein, those with increased serum phosphorus and decreased protein had 11% worse mortality, those with a decrease in both serum phosphorus and protein had 6% worse mortality, and those with decreased serum phosphorus but increased protein had 10% higher survival.[26] Contrary to these studies, a 5-year prospective cohort of 224 hemodialysis patients suggested that higher intake of dietary phosphorus and higher dietary phosphorus-to-protein ratios were both related to increased mortality risk.[27]

Factors Associated with Adherence to Dietary Phosphorus Recommendations

Estimates of non-adherence to phosphorus intake recommendations among dialysis patients have varied from 22% to 81%.[28,29] A number of factors may be related to dietary phosphorus adherence in dialysis patients. The Health Belief Model (HBM) is one of the most widely used theories in health education, being based on the concept that health behaviors are determined by personal perceptions or beliefs about a disease. Several constructs within the HBM have been tested for their association with adherence to a low phosphorus diet in hemodialysis patients. The four most common concepts tested within the HBM include self-efficacy, perceived barriers to diet adherence, perceived benefits of diet adherence, and perceived susceptibility to additional complications with ESRD. Increased self-efficacy correlated with optimal levels of serum phosphorus in hemodialysis patients.[30]

Patients with lower perceptions of barriers are often more likely to adhere to low dietary intake of phosphorus.[31-34] Barriers commonly reported as being problematic included challenges in preparation of special meals, craving foods not allowed on the diet, and having to eat away from home.[33] Hemodialysis patients are more likely to be compliant if they perceived the diet and treatment regimen to be beneficial.[31,33,34] Perceptions of the susceptibility of further complications with ESRD are also associated with increased likelihood of adhering to a low phosphorus diet.[33,34] Even though the connection between these HBM concepts and diet adherence was found in several studies, there have also been studies that have not found any association.[30,33]

Various types of social support have been identified as contributing to adherence to a low phosphorus diet. Some studies have discussed the importance of social support in general or a supportive environment[31,35], while others have highlighted support specifically from family or medical staff.[33,35,36] Increased perceptions of these types of social support were shown to be associated with increased adherence to dietary recommendations. There is also evidence that contradicts the idea that social support is related to dietary adherence in dialysis patients.[33,37] Marital status, a component of social support, varies in its association with adherence to a low phosphorus diet. Some studies suggest that married patients are more compliant[36], whereas other studies propose that not being married is associated with less diet nonadherence.[31,35] It has been suggested that the predictive value of marital social support comes from the adjustment of the patient's spouse to the burden of dialysis and level of marital satisfaction as opposed to being married itself.[38,39] To our knowledge the literature lacks data on the role of race, ethnicity and gender as modifying factors in the relationship between social support and adherence.

The rigorous nature of the medical and dietary treatment for ESRD may be perceived as quite intrusive.[40] For instance, it is known that hemodialysis patients have a high burden of self-care due to having to go to 3-5 hour dialysis treatments three times per week, possibly having to take up to 19 oral pills per day[41], and having to adhere to several dietary and fluid recommendations. This perceived intrusiveness may be different across race and associated with increased levels of depression in this population.[40] It has been estimated that 15-45% of hemodialysis patients are depressed as measured by either self-report or physician diagnosis.[42-44] Depressed hemodialysis patients were found to be twice as likely to be non-adherent to dietary phosphorus recommendations as determined through abnormal serum phosphorus values.[45]

Modifying factors such as patient knowledge have been associated with dietary phosphorus adherence. Non-White patients may be less adherent to low phosphorus recommendations, however, studies investigating associations between race and phosphorus adherence may not have distinguished between Hispanic Whites and non-Hispanic Whites.[30,31] Older hemodialysis patients tend to be more compliant with dietary phosphorus.[30,31] Perhaps older patients have greater adherence because they are used to establishing routines in their daily lives or perhaps they are more concerned and conscious of death.[37] Patient knowledge about chronic kidney disease and their renal diet was positively correlated with diet adherence in several studies[30,31]; however, this finding is not consistent across all hemodialysis populations.[32,33]

Race/Ethnic Differences in Dialysis Patients

Race/ethnicity has been identified as an important factor in the development and course of chronic kidney disease. Hispanics are 1.4 times and African Americans are 3 times more likely to have ESRD and express the need for dialysis, as compared to non-Hispanic whites.[15] Once patients have developed ESRD and are on dialysis, however, Hispanics and African Americans tend have lower rates of mortality than non-Hispanic Whites.[15,46-48]

Age may modify the relationship between race/ethnicity and mortality among ESRD dialysis patients, as a study by Kucirka et al. suggested that Black patients exhibit a survival advantage in the >50-year-old age group.[47] This study, however, did not separate Hispanic and non-Hispanic Whites and combined them as the reference group, which was a major flaw.[46,49] In a later study that distinguished Hispanic ethnicity, Hispanics and Blacks had lower mortality risk than non-Hispanic White dialysis patients, except among 18-30 year olds, where Blacks had worse survival than non-Hispanic Whites.[48] Rhee et al. had a similar observation among over 130,000 ESRD dialysis patients, concluding that Hispanics had the lowest mortality risk compared to non-Hispanic Whites across all age groups.[46] Blacks had a lower mortality risk compared to non-Hispanic Whites only in patients that were older than 40 years. The diminished survival advantage observed in young Black ESRD dialysis patients may be related to inadequate access to health care preceding diagnosis of ESRD, consequently leading to increased comorbidity burden following the initiation of dialysis treatment.[46,47]

Nutritional status and inflammation have been proposed as being mediators of the relationship between race and mortality among ESRD dialysis patients. A combination of malnutrition and inflammation in dialysis patients has been referred to as the malnutrition-inflammation complex syndrome (MICS). In a study of over 124,000 dialysis patients, laboratory surrogates of MICS were measured including serum calcium, serum phosphorus, and normalized protein catabolic rate (nPCR) as a surrogate of dietary protein intake among others.[49] In unadjusted models and case-mix adjusted models, Hispanics and Blacks had lower mortality risk than non-Hispanic Whites. When models were additionally adjusted for MICS, Blacks and Hispanics had similar mortality risk as Whites, except in the >65-year old age group where Hispanics had a survival advantage over Whites.

Given that ethnic and cultural influences have been shown to mediate dietary food choices, perhaps there needs to be more information about dietary intake as a mediator in the race and survival relationship among hemodialysis patients.[50] In a 15-year prospective cohort of over 3,000 participants, Blacks had a higher frequency of eating at fast food restaurants than Whites.[51] Compared to Whites, it has been suggested that Blacks have greater intake of high protein foods such as beef, poultry, fish, pork, and seafood and lower intake of fruits and vegetables.[52] Hispanics have been suggested to consume more fast food, white bread, eggs, and tortillas.[53,54] Higher intakes of fast food and animal proteins from Blacks and Hispanics may be an indication of greater intake of dietary phosphorus.

Assessment of Dietary Intake

Assessment of dietary intake in the general population and in hemodialysis patients is usually conducted using: (1) 24-hour dietary recalls; (2) 3- or 7-day food records with or without a supplementary dietary interview, and (3) food frequency questionnaires (FFQ) that can estimate food intake over several weeks or months.[55] Nearly all studies investigating adherence to dietary phosphorus recommendations in hemodialysis patients use serum phosphorus or subjective self-report measures as a proxy for dietary phosphorus intake.

There are strengths and limitations to each type of dietary assessment. The 24-hour dietary recalls are most commonly used for their convenience and rapid collection of data; however, reports may be susceptible to recall bias and cannot capture possible differences in dietary intake over dialysis and non-dialysis days.[55] Diet records have the advantage of real time recording of dietary intake, yet this method relies heavily on the patients' compliance with the instructions and may be limited by inaccurate or missing entries; but combining the diet records with an interview improves the accuracy.[55] FFQs are relatively convenient and are able to capture typical food intake over long periods of time.[56,57] The primary drawbacks of FFQs include the inability to incorporate all types of available foods and reduced sensitivity to differences among similar types of food. This may be especially relevant with dietary phosphorus, where foods may have significant differences in phosphorus content depending on whether or not inorganic phosphorus additives were added during processing.

Role of the Renal Dietitian

Registered dietitians (RD) play an integral role within the multidisciplinary renal team. Basic responsibilities include assessing patients' diets, evaluating nutritional status, and making dietary recommendations to improve health outcomes. In order for a RD to make an individualized recommendation about what a patient should eat, they should conduct an assessment of the patient's current dietary habits. The KDOQI guidelines recommend for RDs to collect patient dietary intake data biannually with a dietary interview or diary.[58] Unfortunately, many renal dietitians may lack the time and resources to thoroughly make these assessments. In a study by Hand et al, only 6.5% of renal RDs reported assessing patients' dietary intake biannually, while 70% conducted the assessment only when laboratory tests were abnormal.[59] RDs reported lack of software and time as reasons for not conducting dietary assessments more frequently. While 8% of RDs assess diets with a 3-day diet record, 50% used a typical day recall method. Sixty-two percent of RDs analyzed nutrient intakes by estimation "in their head," whereas 24.5% calculated intakes by hand.

Another survey of 848 RDs highlighted the recognition of the KDOQI guidelines within this cohort and barriers to their use.[60] Most of the RDs knew of the guidelines (97%), however, only 58% had read the guidelines in their entirety, and 41% read a portion of the guidelines. Only 5% of respondents utilized all of the guidelines in their clinical practice, whereas 72% had implemented 5 guidelines, 55% had used 10 guidelines, and 92% had used at least one guideline. The dietitians reported several barriers to greater use of the guidelines including poor administrative support from within the dialysis center, not enough time to overcome high RD-to-patient ratios, and limited resources such as food models, computers, and calipers.

Renal dietitians may have an average of 105[60] to 115[61] patients to manage within a dialysis clinic. In addition to the time constraints created by these high RD-to-patient ratios, time for traditional renal activities may be constrained by an increased emphasis on managing mineral bone disease and administrative obligations set by the Centers for Medicare and Medicaid Services.[62] Additional time consuming, yet important, activities reported by RDs include communicating with outside caregivers or family members, managing patient enrollment in pharmacy programs, medical record documentation, coordinating care plans, monthly laboratories, and assessments.[61]

Despite reported inadequacies in time and resources, RDs have been able to improve patient dietary adherence and serum phosphorus concentrations. In an intervention by Sullivan et al., dialysis patients were given a list of phosphorus containing food additives and were instructed to bring this list with them while grocery shopping.[63] The patients were advised to avoid purchasing and eating foods that contained these food additives. If another person was responsible for purchasing the patient's food, then that person was requested to attend the educational session. Patients were also given a list of local fast food restaurants and menu items which contained added phosphorus. Patients were instructed to avoid these foods and were given more appropriate options that fit within the renal diet. During the second month of the study, patients were telephoned to reinforce the recommendations and to have any questions answered. Three months after the initial educational session, patients in the intervention group had a significantly greater decrease in serum phosphorus compared to the control group.

Components of other successful interventions to improve dialysis patient serum phosphorus concentrations include providing individualized education sessions prior to hemodialysis sessions[64], providing information about phosphorus binders and their benefits[65-67], providing information about relevant laboratory tests[65], and use of a variety of educational materials such as colorful booklets[68,69], handouts[67], posters[70], and culturally relevant recipes.[71] Dietitians in qualitative analyses also reported that demonstrating empathy, establishing trust, using simple explanations, and clarifying conflicting information and ambiguities can assist patients in making food choices to maintain healthier levels of serum phosphorus.[72]

Research Approach: Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease Study

Participants

Hemodialysis patients in the current project are participants in the "Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease" (MADRAD) study (study registration: ClinicalTrials.gov; study number NCT01415570). This is an ongoing (2011-2021) prospective cohort study, having collected hemodialysis patient data and outcomes with serial (every 6 months) evaluation rounds since October 2011. Patients have been enrolled in the study using a purposive sampling method. Participants are recruited from UC Irvine Medical Center and 18 different DaVita dialysis clinics in the South Bay-Los Angeles and Orange County areas. These centers have been chosen due to their racially and ethnically diverse populations, with approximately 30% African American, 30% White, 30% Hispanic, and 10% Asian patients.

Patients typically visit the clinics for treatment three times per week – either Tuesday, Thursday, and Saturday or Monday, Wednesday, and Friday. Treatment sessions last anywhere from three to five hours, and patients regularly attend one of four daily shifts in the early morning, mid-day, afternoon, or evening.

Permission for recruitment of patients was organized through the medical directors of the hemodialysis clinics and Dr. Kamyar Kalantar-Zadeh. MADRAD study coordinators, dialysis center staff and nephrologists are relied upon to identify potential participants. Study coordinators then approach these patients to inform them of the study and request their participation. Inclusion criteria include being aged 18 to 85 years and receiving in-center hemodialysis treatment three-times per week for at least 4 weeks. Exclusion criteria include actively receiving peritoneal dialysis, less than 6-month life expectancy, or inability to provide consent without a proxy. The institutional review boards (IRB) of the University of California, Irvine and the Los Angeles Biomedical Research Institute at Harbor-UCLA approved the study protocols. Patients signed an IRB-approved consent form if they agreed to participate, and they were compensated with $20 for each semi-annual set of tests.

Assessment of Dietary Intake via FFQ

As part of the MADRAD study, participants were asked to fill out the Block FFQ[73] at the beginning of their study enrollment and every 6-12 months thereafter. The FFQ booklet contains 152 multiple-choice questions pertaining to 107 food items. The questionnaire asks how often each food/beverage has been consumed in the past several months, with responses ranging from

"Never" to monthly frequencies, weekly frequencies, or daily. Then, based on the days they consume the food/beverage, patients were asked to fill in how much they consume using pictures of portion sizes. All responses were answered by filling in circles with a #2 pencil. While the patients receive hemodialysis treatment at the clinic, dietitians or research assistants supervised the administration of the FFQ. The FFQ was returned to the patient after initial completion if it was noticed that any questions were left unanswered. Following completion, FFQs were scanned with the use of an optical mark reader scanner. The United States Department of Agriculture Nutrient Database was used to analyze the nutrient content of foods/beverages in the FFQ.

Assessment of Dietary Intake via Diet Records with Interviews

A subgroup of MADRAD patients was also requested to complete a 3-day diet record with an interview. Prospective participants were asked if they were interested in completing the diet record. Detailed instructions, lasting about 15 minutes, was provided about how to fill out the diet record, and the patients were given a handout with this information. Instructions included asking the patient to list everything that the patient ate or drank over the upcoming 3 days, including the time, type of food, amount of food, and how it was prepared. Patients were asked to record their food intake as soon as possible after eating in order to keep an accurate record. The use of measuring cups, measuring spoons, and rulers was encouraged to accurately provide the size and amount of food or drink consumed. Patients were also be asked to bring in food labels and/or provide photos (e.g. photos from a smart phone) of nutrition labels of their food and drink items. If the patients had a family member or caregiver that usually prepares or purchases food, the patient was asked for the additional help of this person in filling out the food record to increase accuracy. Patients were informed that they would not be negatively judged by any of their food choices, so as to encourage their normal eating patterns. They were given my email address and phone number in case they had any questions. The *Nutrient Data System for Research* was used to assess the nutritional content of the recorded food items. Patients were interviewed for approximately 15 minutes when they returned their records in order to clarify diet entries.

Assessment of Serum Phosphorus

The KDOQI recommends that hemodialysis patients maintain a serum phosphorus level between 3.5 to 5.5 mg/dL.[6] Hyperphosphatemia is defined as a serum phosphorus > 5.5 mg/dL.[6] Measurements of serum phosphorus were taken in MADRAD monthly.

Structure of Dissertation

In this dissertation, I investigate three research questions related to dietary phosphorus intake and perspectives surrounding dietary behaviors among the cohort of patients enrolled in the MADRAD study. In Chapter 2, I measured the association between total dietary phosphorus intake, phosphorus/1000 kcal, and phosphorus-to-protein ratio and mortality in MADRAD patients. Data from 415 patients who completed a FFQ was analyzed. It was hypothesized that lower intakes of each of these measures of daily dietary phosphorus intake would be associated with an increased risk of all-cause mortality. In Chapter 3, I conducted an exploratory analysis of 3-day diet records from a subgroup of 80 MADRAD patients. I tested associations between patient clinical and sociodemographic characteristics and measures of dietary phosphorus and protein intake. In Chapter 4, I conducted a qualitative analysis investigating patients' perceptions about their diet and clinician-related factors related to dietary adherence. A semi-structured interview was utilized, and a renal staff physician and registered dietitian were observed.

Chapter 2: The Interplay between Dietary Phosphorous and Protein Intake and Mortality in a Prospective Hemodialysis Cohort

Introduction

Hyperphosphatemia is a known predictor of mortality in hemodialysis patients.[74-76] Alterations in serum phosphorus levels have been related to subsequent disruption of parathyroid hormone and calcium homeostasis[77]. These derangements in mineral bone disease may lead to vascular calcification,[78] left ventricular fibrosis and hypertrophy,[79,80] and eventually sudden cardiac death.[81] Hemodialysis often does not sufficiently remove phosphorus to achieve recommended serum phosphorus targets[82], making hyperphosphatemia a frequent occurrence among hemodialysis patients[75,83].

Current clinical practice guidelines advise end-stage renal disease (ESRD) patients treated with dialysis to consume a low phosphorus diet in order to mitigate hyperphosphatemia[84]. However, there is sparse evidence supporting these dietary recommendations. Among existing studies, there have been conflicting reports regarding the impact of dietary phosphorus restriction on outcomes of dialysis patients.[25,27] As lowering dietary phosphorus has the potential to concomitantly reduce intake of heart-healthy macronutrients and micronutrients and heighten the risk of protein energy wasting (PEW),[26,56,85], there has been growing emphasis on dietary liberalization with concurrent use of phosphorus binder medications in the management of hyperphosphatemia in ESRD.

To address this gap in evidence, we sought to examine the associations of specific dietary phosphorus indices, namely total dietary phosphorus intake, phosphorus to energy ratio, and phosphorus to protein ratio, with all-cause mortality risk in a multi-center, prospective cohort of hemodialysis patients of diverse background. We hypothesized that lower intake dietary phosphorus intake is associated with worse survival in this prospective hemodialysis cohort.

Methods

Study Population

The study population was comprised of a prospective cohort of hemodialysis patients from the *Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease* (MADRAD) cohort (ClinicalTrials.gov study: NCT01415570), a prospective study investigating the differential association between nutritional status and dietary factors across racial and ethnic subgroups. Patients in this substudy of the MADRAD cohort were recruited from 16 outpatient hemodialysis clinics in Southern California.

Patients were included provided that they were 1) 18-85 years of age, 2) signed a consent form approved by a local institutional review board, and 3) received at least four consecutive weeks of in-center hemodialysis. Patients were excluded if they were 1) unable to provide consent without a proxy, 2) had a life expectancy less than six months, or 3) were actively receiving peritoneal dialysis treatment. Study approval was obtained from the Institutional Review Boards of the University of California Irvine.

Exposure Ascertainment

The exposure of interest was dietary phosphorus intake as measured by the Block food frequency questionnaire (FFQ). Patients were asked to fill out the Block FFQ at the time of their study enrollment. The FFQ booklet contained 152 multiple-choice questions pertaining to 107 food items. The questionnaire asked how often each food/beverage had been consumed in the past several months, with responses ranging from "Never" to monthly frequencies, weekly frequencies, or daily. Then, based on the days they consume the food/beverage, patients were asked to fill in how much they consume using pictures of portion sizes. The United States

Department of Agriculture Nutrient Database was used to analyze the nutrient content of foods/beverages in the FFQ.

In our primary analyses, we examined the association between daily absolute dietary phosphorus intake categorized as tertiles with all-cause mortality risk. In secondary analyses, we also examined the association between 1) daily dietary phosphorus scaled to energy intake (mg/1000 kcal) and 2) daily dietary phosphorus-to-protein ratio (mg/g) categorized as tertiles with all-cause mortality risk. In sensitivity analyses, we also examined the aforementioned dietary phosphorus indices categorized as quartiles. In order to model the association between dietary phosphorus intake as a continuous variable with all-cause mortality risk, we conducted restricted cubic spline analyses with knots corresponding to the 10th, 50th, and 90th percentiles of observed dietary phosphorus values.

Socio-demographic, Comorbidity, and Dialysis Treatment Data

Baseline socio-demographic and comorbidity were obtained at study entry. The definition of dialysis vintage was the period of time between study entry date and the date of hemodialysis initiation. Standard dialysis laboratory measurements were conducted by Davita on a quarterly or monthly schedule through automated methods. Baseline values of routine laboratory tests, including serum phosphorus, serum albumin, normalized protein catabolic rate (nPCR), and serum creatinine, were used in this study.

Body Anthropometry and Nutritional Measures

Body composition measurements were conducted while patients attended routine hemodialysis treatments. Body mass index (BMI) was calculated using the post-dialysis weight (kg) divided by height-squared (m^2). Daily dietary intake of energy (kcal) and protein (g) were ascertained from the Block FFQ.

Outcome Ascertainment

The primary outcome of interest was all-cause mortality risk. At-risk time began the day after the baseline FFQ administration, and patients were censored for kidney transplantation, transfer to a non-affiliate outpatient dialysis unit or peritoneal dialysis, or at end of the study (February 10, 2018).

Statistical Methods

We estimated the association between dietary phosphorus intake and all-cause mortality risk using Cox proportional hazard models with five incremental levels of covariate adjustment:

(1) *Unadjusted model:* No covariate adjustment;

(2) *Case-mix model:* Covariates in the unadjusted model, as well as age, sex, race (Black vs. Non-Black), ethnicity (Hispanic vs. Non-Hispanic), and diabetes;

(3) *Expanded case-mix model:* Covariates in the case-mix model, as well as vintage, vascular access type, insurance, congestive heart failure, coronary artery disease, combined cardiovascular diseases, and BMI.

We *a priori* defined the expanded case-mix adjusted model as our primary model. To account for the possibility that various dietary and mineral bone disease covariates may be confounders vs. pathway intermediate of dietary phosphorus—mortality associations, we also conducted exploratory models that incrementally adjusted for laboratory, nutritional status, and mineral bone disorder markers using the following models:

(4) *Expanded case-mix+laboratory model:* Covariates in the expanded case-mix model, as well as dialysis adequacy (ascertained by spKt/V), serum albumin, nPCR, serum creatinine, and serum phosphorus;

(5) *Expanded case-mix+laboratory+nutrition:* Covariates in the expanded case-mix + laboratory model, as well as dietary energy intake, and dietary protein intake.

(6) *Expanded case-mix+laboratory+nutrition+mineral and bone disorder model:* Covariates in the expanded case-mix + laboratory + nutrition model, as well as serum calcium and parathyroid hormone levels.

We also conducted analyses examining associations of the dietary phosphorus intake with all-cause mortality across clinically relevant subgroups according to socio-demographics, dialysis treatment characteristics, comorbidities, nutritional status, and mineral bone disorder status. There were no missing data for age, sex, race, ethnicity, vintage, dialysis access, insurance, diabetes, congestive heart failure, coronary artery disease, and combined cardiovascular disease; remaining covariates had <1% missing values except for BMI (3%), serum phosphorus (3%), serum albumin (3%), nPCR (3%), serum creatinine (5%), and spKt/V (6%). Analyses were conducted using STATA version 13.1 (Stata Corp., College Station, TX) and SigmaPlot version 13 (Systat Software, SanJose, CA).

Results

Cohort Description

Among 415 patients, the mean±SD age of the cohort was 55±15 years, among whom 45% were women, 36% were of Black race, 48% were of Hispanic ethnicity, and 55% had diabetes (Table 1.1). The mean and median (IQR) of daily dietary phosphorus intake in the cohort were 834±678 and 695 (372, 1077), respectively. The mean and median (IQR) of daily dietary protein intake in the cohort were 56±47 and 45 (25, 73), respectively. Compared to patients in the lowest absolute dietary phosphorus intake tertile, patients in the highest tertile were more likely to be male, non-Black, or Hispanic; had longer dialysis vintage; were less likely to have underlying diabetes; and were more likely to have combined cardiovascular diseases. Baseline characteristics stratified according to dietary phosphorus scaled to 1000 kcal and dietary phosphorus-to-protein ratio are shown in Supplemental Tables 1.1 and 1.2.

Absolute Dietary Phosphorus Intake and Mortality

Patients contributed a total of 1,425 person-years of follow-up during which 151 death events were observed. Median (IQR) at-risk time was 3.7 (1.9, 5.1) years. In primary analyses of absolute dietary phosphorus intake categorized as tertiles, the lowest tertile of intake was associated with higher mortality risk (ref: highest tertile) in the expanded case-mix model: adjusted HR (aHR) (95%CI) 1.81 (1.19-2.75). Stronger magnitudes of risk were observed with incremental adjustment for laboratory, nutrition, and mineral bone disorder covariates: aHRs (95%CIs) 1.96 (1.27-3.02), 3.33 (1.75-6.33), and 3.35 (1.76-6.39) in the expanded case-mix+laboratory, expanded case-mix+laboratory+nutrition, and expanded case-mix+laboratory+nutrition+mineral bone disorder analyses, respectively (Figure 1.1(A) and Supplemental Table 1.3).

In sensitivity analyses of absolute dietary phosphorus intake categorized as quartiles, the lowest quartile of intake was associated with higher mortality risk (ref: highest quartile) in the expanded case-mix model: aHR (95%CI) 1.65 (1.02-2.69). Stronger magnitudes of risk were observed with incremental adjustment for laboratory, nutrition, and mineral bone disorder covariates: aHRs (95%CIs) 1.93 (1.16-3.20), 3.20 (1.44-7.15), and 3.32 (1.48-7.42) in the expanded case-mix+laboratory, expanded case-mix+laboratory+nutrition, and expanded case-mix+laboratory+nutrition+mineral bone disorder analyses, respectively (Figure 1.1(B) and Supplemental Table 1.4).

In restricted cubic spline analyses that examined the association of absolute dietary phosphorus as a continuous variable and mortality risk with adjustment for expanded case-mix covariates, there was a monotonic increase in death risk with lower levels of intake (Figure 1.2(A)).

Dietary Phosphorus Intake Scaled to Energy Intake and Mortality

In secondary analyses of dietary phosphorus scaled to energy intake (mg/1000 kcal) categorized as tertiles, the lowest tertile was associated with higher mortality risk in the expanded case-mix+laboratory+nutrition and expanded case-mix+laboratory+nutrition+mineral bone disorder models (ref: highest tertile): aHRs (95% CI) 1.74 (1.08-2.80) and 1.73 (1.07-2.80), respectively (Figure 1.3(A) and Supplemental Table 1.3). In sensitivity analyses of dietary phosphorus scaled to energy intake categorized as quartiles, the lowest quartile of intake was associated with higher mortality risk in the expanded case-mix+laboratory+nutrition and expanded case-mix+laboratory+nutrition+mineral bone disorder models (ref: lowest quartile): aHRs (95%CIs) 1.80 (1.05-3.09), 1.80 (1.05-3.11), respectively (Figure 1.3(B) and Supplemental Table 1.3). In restricted cubic spline analyses that examined the association of dietary phosphorus scaled to energy intake as a continuous variable and mortality risk with adjustment for expanded case-mix covariates, there was a monotonic increase in death risk with lower levels of intake (Figure 1.2(B)).

Dietary Phosphorus-to-Protein Ratio and Mortality

In secondary analyses of dietary phosphorus-to-protein ratio (mg/g) categorized as tertiles, the lowest tertile of intake was associated with higher mortality risk in the expanded case-mix+laboratory+nutrition and expanded case-mix+laboratory+nutrition+mineral bone disorder models (ref: highest tertile): aHRs (95% CIs) 1.67 (1.02-2.74) and 1.65 (1.00-2.72), respectively (Figure 1.4(A) and Supplemental Table 1.3). In sensitivity analyses of dietary phosphorus-to-protein ratio intake categorized as quartiles, point estimates of the lowest quartile of intake trended towards higher mortality risk in the expanded case-mix+laboratory+nutrition and expanded case-mix+laboratory+nutrition+mineral bone disorder models but did not achieve statistical significance (ref: highest tertile): aHRs (95% CI) 1.11 (0.62, 1.98) and 1.14 (0.63, 2.05), respectively (Figure 1.4(B) and Supplemental Table 1.3). In restricted cubic spline analyses that examined the association of dietary phosphorus-to-protein ratio as a continuous variable and mortality risk with adjustment for expanded case-mix covariates, there was a monotonic increase in death risk with lower levels of intake (Figure 1.2(C)).

Absolute Dietary Phosphorus Intake and Mortality Across Clinically Relevant Subgroups

In expanded case-mix analyses of absolute dietary phosphorus intake and mortality risk across clinically relevant subgroups, we detected effect modification on the basis of age (p-interaction=0.03), such that the lowest tertile of intake was associated with higher mortality risk in those who were of older age (≥60 years old) but not in those of younger age (<60 years old): aHRs (95%CI) 2.63 (1.62, 4.29) and 0.97 (0.57, 1.66), respectively (Figure 1.5 and Supplemental Table 1.5). We did not detect effect modification on the basis of sex, race, ethnicity, vintage, vascular access type, insurance status, BMI, diabetes status, cardiovascular disease status, serum phosphorus, serum albumin, serum creatinine, nPCR, spKt/V, of dietary protein intake levels. In all subgroups the nominal HRs for mortality for the lowest tertile of absolute dietary phosphorus intake were >1 except among patients who were <60 years of age. Nominal associations were statistically significant who were ≥60 years old, female, non-Black, or Hispanic; with vintage ≥2 years, with a AV fistula/graft, without tunneled catheter, or with a non-Medicare/Medicaid source as their primary insurance; with BMI <30 or ≥30 kg/m^2; with underlying diabetes or combined cardiovascular diseases; with serum phosphorus levels <5.5 mg/dl, albumin levels ≥4 g/dl, creatinine <median of observed values, nPCR <1 g/kg/day, or spKt/v <1.4 or ≥1.4; or dietary protein intake <median or ≥median levels of observed vales.

Discussion

In this multi-center prospective cohort of maintenance hemodialysis patients, we observed that those with lower dietary phosphorus intake had higher mortality risk. These associations were robust across multiple secondary analyses examining various dietary phosphorus indices and sensitivity analyses examining potential confounders and clinically relevant subgroups.

Given the established association of high serum phosphorus levels with worse survival among hemodialysis patients, clinical practice recommendations often promote dietary phosphorus restriction as a means to mitigate hyperphosphatemia. However, according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines, there is low quality evidence in support of this practice therefore making it a weak recommendation.[84] By limiting dietary phosphorus intake, patients may concomitantly reduce consumption of other critical nutrients such as protein, fat, complex carbohydrates, fiber, and various vitamins and minerals. Observational dietary studies of dialysis patients have suggested dietary restrictions are associated with decreased consumption of fruits and vegetables[56] and overall fiber.[85] Hence, the reduction of these heart-healthy nutrients may increase risk of cardiovascular morbidity and mortality.[85]

Other observational studies have suggested that reduced dietary phosphorus intake may have adverse implications upon dialysis patient outcomes. In a secondary analysis of the HEMO study by Lynch and colleagues, prescribed low dietary phosphorus intake was not associated with a survival benefit among hemodialysis patients, suggesting that dietary phosphorus restriction may be potentially harmful.[25] In another study of over 30,000 hemodialysis patients by Shinaberger and colleagues, compared to patients with a six-month increase in serum phosphorus levels and dietary protein intake, those with increased serum phosphorus levels and decreased protein intake had 11% higher death risk than those with a concomitant decrease in both serum phosphorus and protein intake had 6% higher death risk, and those with decreased serum phosphorus but increased protein intake had 10% greater survival.[26] In contrast to these studies, a five-year prospective cohort of 224 hemodialysis patients by Noori et al., suggested that higher intake of dietary phosphorus and higher dietary phosphorus-to protein ratios were both associated with higher mortality risk.[27]

Our study's findings in this contemporary, diverse cohort of hemodialysis patients underscore the potential ill effects of dietary phosphorus restriction upon the health and survival of the ESRD population. Given the paramount importance of adequate nutritional status in hemodialysis patients, who are prone to hypercatabolism, protein and amino acid losses via dialysis, and protein-energy wasting, the risk of dietary phosphorus restriction may outweigh its benefits, particularly if it leads to reduction in dietary protein intake and other heart-healthy nutrients.[86] Hence, rather than imposing strict dietary regimens including dietary phosphorus restriction in the management of hyperphosphatemia, it may be more prudent to recommend a more liberal diet with ample use of phosphorus binders with stronger binding capacities in the ESRD population.[87,88]

Another notable observation in our study was the differential association between dietary phosphorus intake and survival across hemodialysis patients of older vs. younger age. Whereas lower dietary phosphorus intake was associated with a 2.6-fold higher death risk in patients ≥60 years of age, it was not associated with mortality in those <60 years old. One potential explanation for these findings may be that inadequate nutritional status is more prevalent in elderly hemodialysis patients,[89] who may be more vulnerable to protein-energy wasting. Another possible explanation may be related to the sources of phosphorus intake across age groups (i.e., organic vs. inorganic). Organic sources of phosphorus, such as plant-based and animal-based sources, may have absorption rates ranging from approximately <40% to 60%, whereas inorganic added phosphorus absorption may be 80-100%.[90]. These inorganic phosphorus additives are commonly found in processed fast and convenience foods, and elderly CKD populations may consume higher amounts of convenience foods due to socio-economic and/or functional (i.e., activities of daily living) limitations.[91] Even with similar amounts of dietary phosphorus intake, the bioavailability of the phosphorus will dictate the effect on serum phosphorus and therefore mortality, and further study of the different effects of dietary intake across age in ESRD are needed.

The strengths of our study include its availability of detailed patient-level data on sociodemographic, nutritional status, comorbidity, and laboratory data information from a contemporary, multi-center cohort of hemodialysis patients, as well as rigorous, protocolized collection of FFQ over time. However, there are several limitations that should be mentioned.

First, responses to the FFQ are self-reported and may have been subject to under- or over-estimation of actual dietary intake. Second, the FFQ is unable to list every type of food typically eaten by hemodialysis patients and therefore some phosphorus-containing foods may be under-reported in the questionnaire. Third, the FFQ analysis of nutrients does not differentiate organic versus inorganic phosphorus, which did not allow for discernment of type of phosphorus in our analyses. Lastly, due to the observational nature of our study, we cannot confirm a causal association between dietary phosphorus intake and mortality.

In conclusion, our study suggests that lower dietary phosphorus intake is associated with higher risk of all-cause mortality in a prospective cohort of hemodialysis patients. Further studies are needed to determine the impact of the differential sources of dietary phosphorus, as well as alternative strategies that can mitigate hyperphosphatemia without compromising nutritional status upon the health outcomes of the ESRD population.

Table 1.1. Baseline characteristics of hemodialysis patients according to daily absolute dietary phosphorus intake categories (N=415).

	Overall	Dietary Phosphorus Intake (mg/day)		
		Tertile 1	Tertile 2	Tertile 3
N (%)	415	138	137	140
Age (mean ± SD)	55 ± 15	57 ± 15	57 ± 13	53 ± 15
Male (%)	55	41	58	66
Black race (%)	36	35	34	40
Hispanic ethnicity (%)	48	46	47	52
Vintage (years, mean ± SD)	5 ± 4	4 ± 3	5 ± 4	5 ± 5
BMI (kg/m2, mean ± SD)	27.6 ± 6.6	27.4 ± 6.6	27.5 ± 6.0	27.9 ± 7.0
spKt/V	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.4
Dialysis access				
AV Fistula/Graft	47	39	50	53
Catheter	11	11	12	10
Unknown	41	50	37	37
Insurance				
Medicare/Medicaid	75	76	77	73
Private	11	13	12	9
Other	14	11	12	19
COMORBIDITIES				
Diabetes (%)	55	59	50	55
CHF (%)	8	9	7	9
CAD (%)	9	8	9	10
Combined CV disease (%)	17	16	15	19
LABORATORY RESULTS				
Serum phosphorus (mg/dL)	5.1 ± 1.5	5.1 ± 1.4	5.0 ± 1.3	5.1 ± 1.6
Serum albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.4
nPCR (g/kg/day)	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3
Serum creatinine (mg/dL)	9.7 ± 3.0	9.5 ± 3.1	9.6 ± 2.6	10.2 ± 3.1
DIETARY INTAKE				
Energy (kcal/day)	998(566, 1527)	446 (302, 596)	1006 (842, 1252)	1790 (1398, 2373)
Protein (g/day)	45 (25, 73)	20 (14, 25)	45 (36, 55)	84 (69, 124)

BMI, body mass index; AV, arteriovenous; CHF, congestive heart failure; CAD, coronary artery disease; CV, cardiovascular; nPCR, normalized protein catabolic rate.

Figure 1.1. Association between daily absolute dietary phosphorus intake and all-cause mortality among hemodialysis patients across tertiles (Panel A) and quartiles (Panel B).

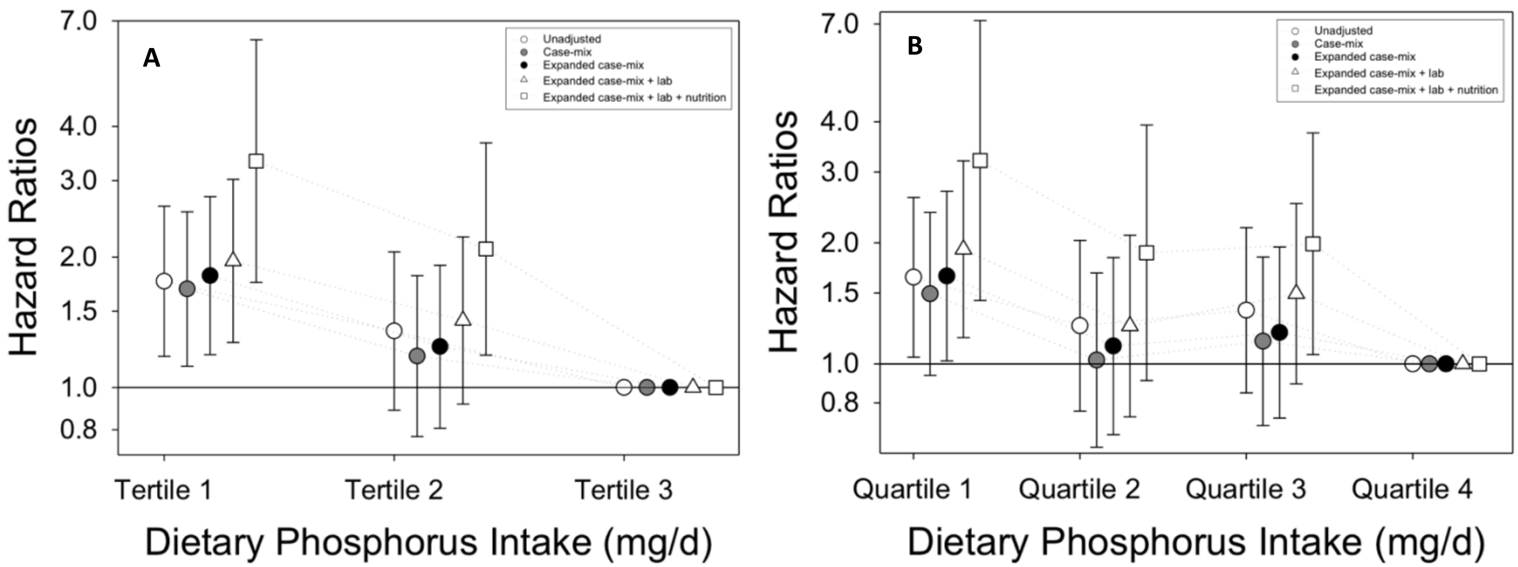


Figure 1.2. Association between baseline daily dietary phosphorus as a continuous variable and all-cause mortality among 415 MADRAD hemodialysis patients using restricted cubic spline analysis. Knots placed at the 10th, 50th, and 90th percentiles of observed values.

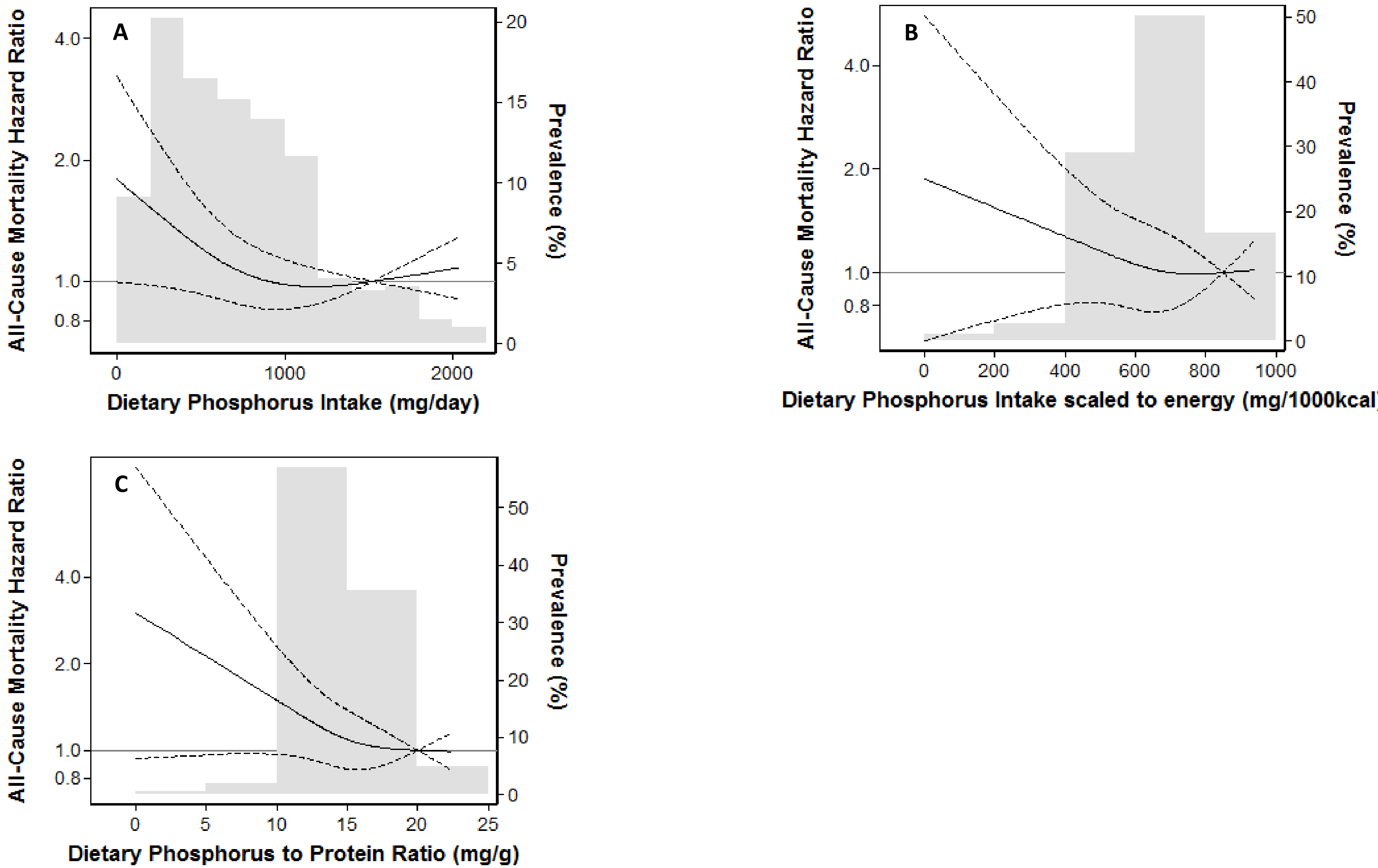


Figure 1.3. Association between daily dietary phosphorus intake scaled to 1000 kcal and all-cause mortality among hemodialysis patients across tertiles (Panel A) and quartiles (Panel B)

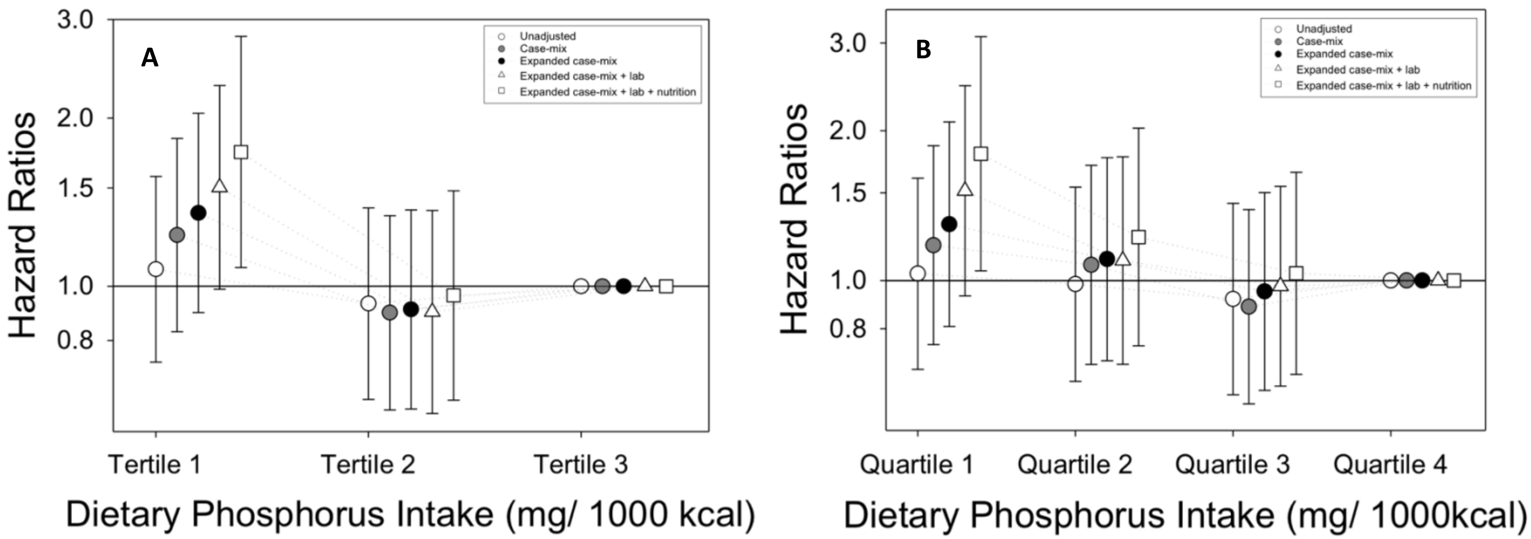


Figure 1.4. Association between daily dietary phosphorus-to-protein ratio and all-cause mortality among hemodialysis patients across tertiles (Panel A) and quartiles (Panel B).

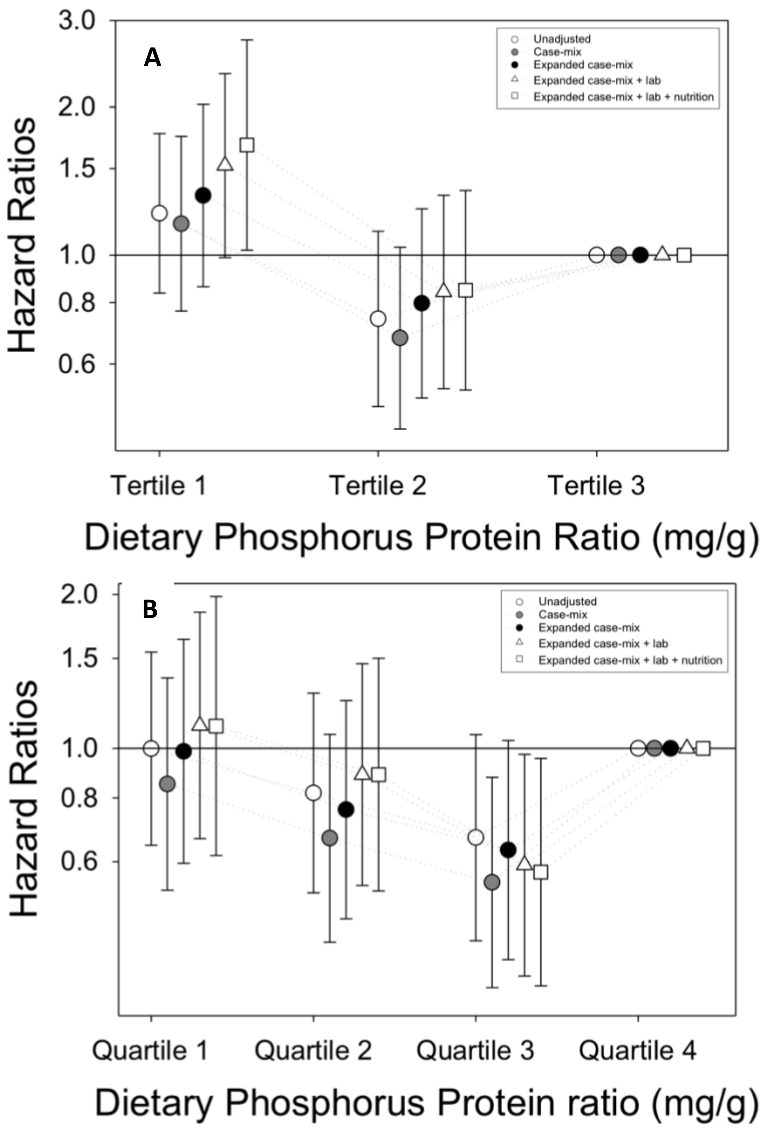
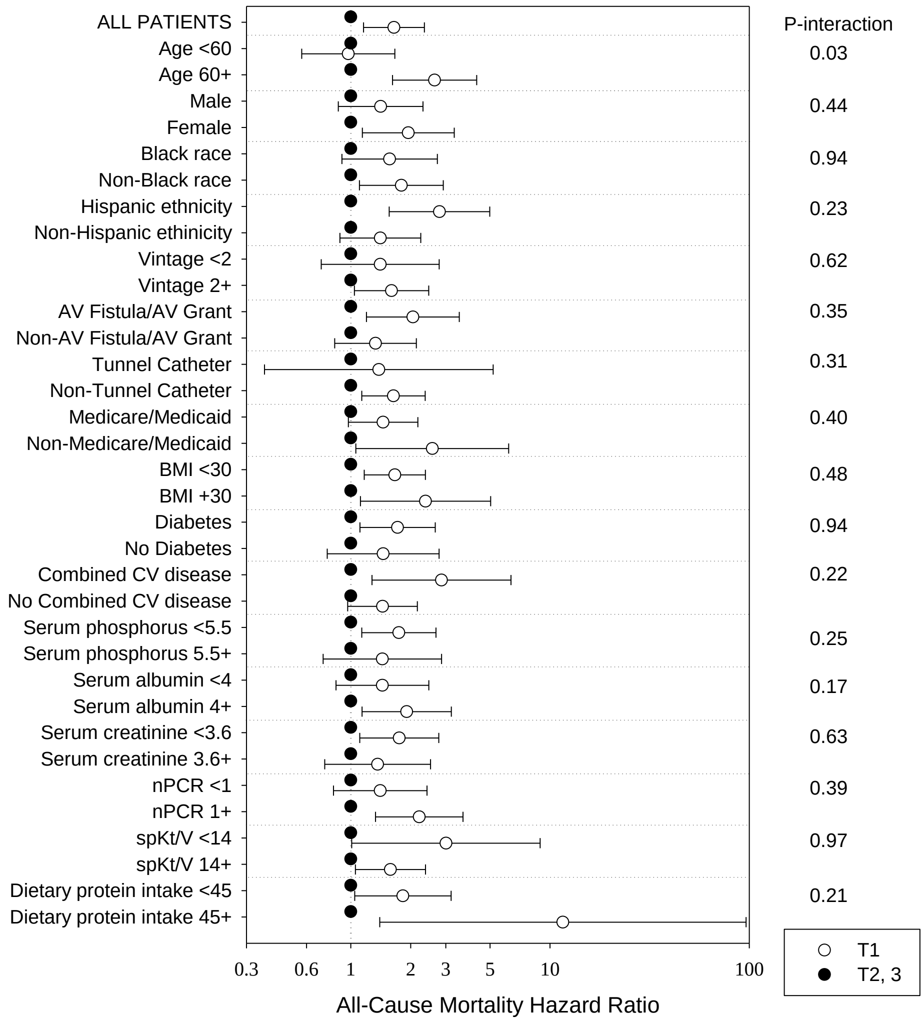


Figure 1.5. Association between lowest tertile of daily dietary phosphorus intake (ref: middle and highest tertiles) and all-cause mortality in hemodialysis patients across clinically relevant subgroups using expanded case-mix adjusted analyses.



Supplemental Table 1.1. Baseline characteristics of hemodialysis patients according to daily dietary phosphorus intake scaled to 1000 kcal.

	Overall	Dietary Phosphorus Intake (mg/1000 kcal)		
		Tertile 1	Tertile 2	Tertile 3
N (%)	415	138	138	139
Age (mean ± SD)	55±15	55±14	55±15	56±15
Male (%)	55	55	52	59
Black race (%)	36	33	43	32
Hispanic ethnicity (%)	48	40	46	60
Vintage (years, mean ± SD)	5±4	5±4	5±4	4±4
BMI (kg/m2, mean ± SD)	27.6±6.6	27.5±7.2	28.5±6.7	26.9±5.6
spKt/V	1.7±0.3	1.7±0.4	1.7±0.3	1.7±0.3
Dialysis access				
AV Fistula/Graft	47	49	54	40
Catheter	11	12	8	14
Unknown	41	40	38	46
Insurance				
Medicare/Medicaid	75	80	73	73
Private	11	9	13	12
Other	14	12	14	16
COMORBIDITIES				
Diabetes	55	46	51	66
CHF	8	5	10	10
CAD	9	12	9	6
Combined CV disease	17	15	20	16
LABORATORY RESULTS				
Serum phosphorus (mg/dL)	5.1±1.5	5.1±1.5	5.1±1.5	5.0±1.4
Serum albumin (g/dL)	4.0±0.4	4.1±0.3	4.0±0.3	4.0±0.4
nPCR (g/kg/day)	1.0±0.3	1.0±0.3	1.0±0.3	1.1±0.3
Serum creatinine (mg/dL)	9.7±3.0	9.9±2.9	9.9±3.0	9.5±2.9
DIETARY INTAKE				
Energy (kcal/day)	998(566,1,527)	891(480,1,512)	1,108(608,1,596)	1,078(676,1,466)
Protein (g/day)	45(25,73)	32(19,60)	46(27,78)	53(33,80)

BMI, body mass index; AV, arteriovenous; CHF, congestive heart failure; CAD, coronary artery disease; CV, cardiovascular; nPCR, normalized protein catabolic rate.

Supplemental Table 1.2. Baseline characteristics of hemodialysis patients according to daily dietary phosphorus-to-protein intake (mg/g).

	Overall	Dietary Phosphorus Intake (mg/g)		
		Tertile 1	Tertile 2	Tertile 3
N (%)	415	138	138	139
Age (mean ± SD)	55±15	54±15	56±15	56±14
Male (%)	55	53	62	52
Black race (%)	36	41	46	22
Hispanic ethnicity (%)	48	29	41	75
Vintage (years, mean ± SD)	5±4	4±4	5±4	5±4
BMI (kg/m2, mean ± SD)	27.6±6.6	27.2±6.7	28.6±7.1	27.0±5.7
spKt/V	1.7±0.3	1.7±0.3	1.7±0.3	1.8±0.4
Dialysis access				
AV Fistula/Graft	47	49	47	46
Catheter	11	12	9	12
Unknown	41	38	43	42
Insurance				
Medicare/Medicaid	75	75	73	78
Private	11	14	11	9
Other	14	12	16	14
COMORBIDITIES				
Diabetes	55	53	51	60
CHF	8	7	9	10
CAD	9	11	9	8
Combined CV disease	17	16	16	19
LABORATORY RESULTS				
Serum phosphorus (mg/dL)	5.1±1.5	5.3±1.4	4.8±1.4	5.1±1.6
Serum albumin (g/dL)	4.0±0.4	4.0±0.3	4.0±0.4	4.0±0.3
nPCR (g/kg/day)	1.0±0.3	1.1±0.3	1.0±0.3	1.0±0.3
Serum creatinine (mg/dL)	9.7±3.0	10.0±3.0	10.0±2.9	9.2±2.9
DIETARY INTAKE				
Energy (kcal/day)	998(566,1,527)	1,107(641,1,701)	938(547,1,424)	998(632,1,464)
Protein (g/day)	45(25,73)	60(31,93)	46(24,67)	39(22,58)

BMI, body mass index; AV, arteriovenous; CHF, congestive heart failure; CAD, coronary artery disease; CV, cardiovascular; nPCR, normalized protein catabolic rate.

Supplemental Table 1.3. Association between dietary phosphorus intake and all-cause mortality in hemodialysis patients across tertiles (ref: highest tertile).

Dietary Phosphorus Intake (mg/day)*						
	Unadjusted	Case-mix adjusted	Expanded case-mix adjusted	Expanded case-mix+laboratory adjusted	Expanded case-mix+laboratory+ nutrition adjusted	Expanded case-mix+laboratory+ nutrition+MBD adjusted
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Tertile 1	1.76(1.18,2.62)	1.69(1.12,2.54)	1.81(1.19,2.75)	1.96(1.27,3.02)	3.33(1.75,6.33)	3.35(1.76,6.39)
Tertile 2	1.35(0.89,2.06)	1.18(0.77,1.81)	1.24(0.81,1.91)	1.43(0.92,2.23)	2.09(1.19,3.67)	2.10(1.19,3.71)
Tertile 3	Reference	Reference	Reference	Reference	Reference	Reference
P-trend	0.005	0.011	0.005	0.002	<0.001	<0.001
Dietary Phosphorus Intake Scaled to 1000 kcal (mg/1000 kcal)**						
	Unadjusted	Case-mix adjusted	Expanded case-mix adjusted	Expanded case-mix+laboratory adjusted	Expanded case-mix+laboratory+ nutrition adjusted	Expanded case-mix+laboratory+ nutrition+MBD adjusted
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Tertile 1	1.07(0.73,1.57)	1.24(0.83,1.84)	1.35(0.90,2.04)	1.50(0.99,2.29)	1.74(1.08,2.80)	1.73(1.07,2.80)
Tertile 2	0.93(0.63,1.38)	0.90(0.60,1.34)	0.91(0.60,1.37)	0.90(0.59,1.37)	0.96(0.63,1.48)	0.98(0.63,1.51)
Tertile 3	Reference	Reference	Reference	Reference	Reference	Reference
P-trend	0.733	0.335	0.185	0.078	0.033	0.034
Dietary Phosphorus-to-Protein Ratio (mg/g)***						
	Unadjusted	Case-mix adjusted	Expanded case-mix adjusted	Expanded case-mix+laboratory adjusted	Expanded case-mix+laboratory+ nutrition adjusted	Expanded case-mix+laboratory+ nutrition+MBD adjusted
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Tertile 1	1.22(0.84,1.77)	1.16(0.77,1.74)	1.32(0.86,2.03)	1.52(0.99,2.34)	1.67(1.02,2.74)	1.65(1.00,2.72)
Tertile 2	0.74(0.49,1.12)	0.68(0.44,1.04)	0.80(0.51,1.24)	0.84(0.53,1.32)	0.85(0.53,1.35)	0.84(0.52,1.34)

Tertile 3	Reference	Reference	Reference	Reference	Reference	Reference
P-trend	0.308	0.436	0.166	0.045	0.037	0.044

MBD, Mineral and bone disorder.

* Tertiles for dietary phosphorus correspond to <460, 463-<933, and 943-4992 mg/day, respectively.

** Tertiles for dietary phosphorus scaled to 1000 kcal (mg/1000 kcal) correspond to <606, 607-<736, and 737-1153 mg/1000 kcal, respectively.

*** Tertiles for dietary phosphorus-to-protein ratio correspond to intake of <13.4, 13.5-<15.93, and 15.95-57.5 mg/g, respectively.

Supplemental Table 1.4. Association between dietary phosphorus intake and all-cause mortality in hemodialysis patients across quartiles (ref: highest quartile).

Dietary Phosphorus Intake (mg/day)						
	Unadjusted	**Case-mix adjusted**	**Expanded case-mix adjusted**	**Expanded case-mix+laboratory adjusted**	**Expanded case-mix+laboratory+ nutrition adjusted**	**Expanded case-mix+laboratory+ nutrition+MBD adjusted**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Quartile 1	1.64(1.04,2.59)	1.49(0.94,2.38)	1.65(1.02,2.69)	1.93(1.16,3.20)	3.20(1.44,7.15)	3.32(1.48,7.42)
Quartile 2	1.24(0.76,2.03)	1.02(0.62,1.68)	1.11(0.67,1.84)	1.24(0.74,2.09)	1.89(0.91,3.93)	1.90(0.91,3.97)
Quartile 3	1.36(0.85,2.18)	1.14(0.70,1.84)	1.20(0.73,1.95)	1.49(0.89,2.51)	1.99(1.05,3.75)	2.05(1.08,3.90)
Quartile 4	Reference	Reference	Reference	Reference	Reference	Reference
P-trend	0.055	0.131	0.062	0.029	0.01	0.009
Dietary Phosphorus Intake Scaled to 1000 kcal (mg/1000 kcal)						
	Unadjusted	**Case-mix adjusted**	**Expanded case-mix adjusted**	**Expanded case-mix+laboratory adjusted**	**Expanded case-mix+laboratory+ nutrition adjusted**	**Expanded case-mix+laboratory+ nutrition+MBD adjusted**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Quartile 1	1.03(0.66,1.61)	1.18(0.74,1.87)	1.30(0.81,2.08)	1.51(0.93,2.46)	1.80(1.05,3.09)	1.80(1.05,3.11)
Quartile 2	0.98(0.63,1.54)	1.08(0.68,1.70)	1.10(0.69,1.77)	1.10(0.68,1.77)	1.22(0.74,2.02)	1.22(0.73,2.02)
Quartile 3	0.92(0.59,1.43)	0.89(0.57,1.39)	0.95(0.60,1.50)	0.97(0.61,1.55)	1.03(0.65,1.65)	1.03(0.64,1.64)
Quartile 4	Reference	Reference	Reference	Reference	Reference	Reference
P-trend	0.837	0.38	0.246	0.101	0.039	0.04
Dietary Phosphorus-to-Protein Ratio (mg/g)						

	Unadjusted	Case-mix adjusted	Expanded case-mix adjusted	Expanded case-mix+laboratory adjusted	Expanded case-mix+laboratory+ nutrition adjusted	Expanded case-mix+laboratory+ nutrition+MBD adjusted
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Quartile 1	1.00(0.65,1.54)	0.85(0.53,1.37)	0.99(0.60,1.63)	1.11(0.67,1.85)	1.11(0.62,1.98)	1.14(0.63,2.05)
Quartile 2	0.82(0.52,1.28)	0.67(0.42,1.07)	0.76(0.46,1.24)	0.89(0.54,1.46)	0.89(0.53,1.50)	0.89(0.53,1.51)
Quartile 3	0.67(0.42,1.06)	0.55(0.34,0.88)	0.63(0.39,1.04)	0.59(0.36,0.97)	0.57(0.34,0.96)	0.59(0.35,0.99)
Quartile 4	Reference	Reference	Reference	Reference	Reference	Reference
P-trend	0.775	0.787	0.767	0.328	0.375	0.376

MBD, Mineral and bone disorder

* Dietary phosphorus intake quartiles 1, 2, 3 and 4 correspond to dietary phosphorus intake of <370, 372-<695, 695-<1064, and 1077-4992 mg/day, respectively.

** Dietary phosphorus/1000 kcal quartiles 1, 2, 3 and 4 correspond to intakes of <573, 574-<674.8, 674.9-<774, and 777-1153 mg/1000 kcal, respectively.

*** Dietary phosphorus-to-protein ratio quartiles 1, 2, 3 and 4 correspond to intakes of <12.9, 12.9-<14.6, 14.6-<17.03, and 17.03-57.5 mg/g, respectively.

Supplemental Table 1.5. Association between lowest tertile of dietary phosphorus intake (ref: middle and highest tertiles) and all-cause mortality in hemodialysis patients across clinically relevant subgroups using expanded case-mix adjusted analyses.

	DIETARY PHOSPHOROUS INTAKE		
SUBGROUPS	**Tertile 1**	**Tertiles 2+3**	**p**
Age			
<60 years	0.97(0.57,1.66)	Reference	0.03
≥60 years	2.63(1.62,4.29)		
Sex			
Female	1.94(1.14,3.31)	Reference	0.44
Male	1.41(0.87,2.30)		
Race			
Non-Black	1.79(1.11,2.91)	Reference	0.94
Black	1.57(0.90,2.72)		
Hispanic ethnicity			
Yes	2.79(1.56,4.98)	Reference	0.23
No	1.41(0.88,2.25)		
Vintage (years)			
<2	1.41(0.71,2.78)	Reference	0.62
≥2	1.60(1.04,2.46)		
AV Fistula/AV Grant			
Yes	2.05(1.20,3.50)	Reference	0.35
No	1.33(0.83,2.13)		
Tunnel Catheter			
Yes	1.38(0.37,5.18)	Reference	0.31
No	1.64(1.14,2.36)		
Medicare/Medicaid			
Yes	1.45(0.97,2.17)	Reference	0.4
No	2.57(1.06,6.21)		
BMI (kg/m$_2$)			
<30	1.66(1.17,2.37)	Reference	0.48
≥30	2.37(1.12,5.03)		
Diabetes			
Yes	1.72(1.11,2.65)	Reference	0.94
No	1.45(0.76,2.77)		
Combined CV Disease	2.85(1.28,6.37)	Reference	0.22

Yes No	1.44(0.96,2.16)		
Serum phosphorus (mg/dL) <5.5 ≥5.5	1.74(1.13,2.67) 1.44(0.73,2.86)	Reference	0.25
Serum albumin (g/dL) <4 ≥4	1.44(0.84,2.46) 1.91(1.14,3.20)	Reference	0.17
Serum creatinine (mg/dL) <9.6 ≥9.6	1.75(1.11,2.77) 1.36(0.74,2.51)	Reference	0.63
nPCR (g/kg/day) <1 ≥1	1.41(0.82,2.41) 2.21(1.33,3.66)	Reference	0.39
spKt/V <1.4 ≥1.4	3.00(1.01,8.93) 1.58(1.05,2.37)	Reference	0.97
Protein (g/day) <45 (median) ≥45 (median)	1.83(1.05,3.19) 11.61(1.40,96.39)	Reference	0.21

BMI, body mass index; AV, arteriovenous; CV, cardiovascular; nPCR, normalized protein catabolic rate.

Chapter 3: Patient Characteristics and Dietary Phosphorus and Protein Intake among an Ethnically and Racially Diverse Cohort of Hemodialysis Patients

Introduction

Regulation of phosphorus intake through food is of particular importance due to evidence that hyperphosphatemia is associated with an increased risk of mortality in hemodialysis patients.[1-3] The Kidney Disease Outcome Quality Initiative (KDOQI) guidelines define hyperphosphatemia in hemodialysis patients as having serum phosphorus > 5.5 mg/dL.[5,6] Hemodialysis patients are advised to have a maximum of up to 800-1000 mg of phosphorus per day to prevent hyperphosphatemia[92], as compared to the Recommended Dietary Allowance for phosphorus in healthy adults, which is 700 mg/day with an Upper Limit of 4000 mg/day.[7] Even within the general population, elevated levels of dietary phosphorus intake >1400 mg/day have been associated with increased risk of all-cause mortality.[8]

Most foods contain some amount of phosphorus, however, it is naturally abundant in foods that are good sources of protein.[16] The bioavailability of phosphorus, the fraction of ingested phosphorus that is absorbed through the intestines, ranges from 20% to nearly 100% and depends on several variables. These factors include the source of phosphorus, i.e., organic plant protein vs. organic animal protein vs. inorganic or added P and the influence of such factors as vitamin D, which may modify the amount P absorbed via the intestines.

The bioavailability of organic phosphorus from animal-based proteins is moderate, with 40 to 60% of the phosphorus being absorbed in the intestines.[18] While in the intestines, organic P is broken down into organic PO_4 and absorbed into the bloodstream. Sources of phosphorus in animal-based protein include chicken, fish, seafood, dairy, and red meat.

Plant proteins include nuts, legumes, seeds, and grains. Whereas the phosphorus in animal protein is readily degraded and absorbed, the phosphorus in plant proteins is mostly found in the less accessible form of phytate or phytic acid. Humans do not express the enzyme phytase to effectively digest phytates, therefore leading to lower rates of absorption in plant proteins. Consequently, phosphorus bioavailability from plants is relatively low, with approximately 20-40% absorption.[19]

Since there is much greater bioavailability of inorganic phosphorus, this type of dietary phosphorus may have a larger influence on hyperphosphatemia in hemodialysis patients than an equal amount of dietary organic phosphorus.[20] Inorganic phosphorus is not naturally found in foods, but is usually found as an additive in processed foods and fast foods. It serves many purposes including extending shelf life, improving the color of food, enhancing flavor, and helps to retain moisture.[19,21] It is found in a variety of food products including fast foods, colas, cereals, processed cheeses, instant products, and deli meats.[22] As opposed to organic phosphorus, inorganic phosphorus is not bound to protein; therefore, it is easily and readily absorbed through the intestines. It has been estimated that 90-100% of inorganic phosphorus additives are absorbed and they contribute up to 1000 mg per day of daily dietary phosphorus.[23,24]

Estimates of non-adherence to phosphorus intake recommendations among dialysis patients have varied from 22% to 81%, and may be related to various modifiable and non-modifiable patient characteristics.[22,23] To gain insight into dietary phosphorus intakes and related dialysis patient clinical and sociodemographic characteristics, we analyzed data from 3-day diet records collected from a diverse cohort of patients within the Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.

Methods

Study Population

Study participants were a subgroup of hemodialysis patients enrolled in the Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease (MADRAD) study, a prospective cohort study exploring the relationship between dietary factors and nutritional status across racial and ethnic subgroups. Patients in this cohort were recruited from December 2018 to December 2019 from 13 outpatient hemodialysis clinics in Southern California.

Patients were requested to complete a 3-day diet record with an interview. Detailed instructions were provided about how to fill out the diet record, and the patients were given a handout with this information. Instructions included listing everything that the patient eats or drinks for 3 days, including the time, type of food, amount of food, and how it was prepared. Patients were asked to record their food intake as soon as possible after eating in order to keep an accurate record. If the patients have a family member or caregiver that usually prepares or purchases food, the patient was additionally requested to enlist the help of this person in filling out the diet record to increase accuracy. Patients were interviewed when they returned their diet records in order to clarify entries.

Patients were included in the study if they were 18-85 years of age, signed a consent form approved by a local institutional review board, and had received at least four consecutive weeks of thrice-weekly in-center hemodialysis. Patients were excluded if they were unable to provide consent without a proxy, were actively receiving peritoneal dialysis treatment, or had less than six months life expectancy. The study was approved by the institutional review boards of the Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA, and the University of California Irvine Medical Center, Orange, CA.

Dialysis Treatment, Socio-demographic, and Comorbidity Measures

Dialysis treatment, socio-demographic, and comorbidity measures were recorded. Vintage was defined as the span of time between the date that hemodialysis was initiated and entrance into the study.

Body Anthropometry and Nutritional Measures

Measurements of body composition were obtained during the patients' regular hemodialysis treatments. Calculations for body mass index (BMI) used the post-dialysis weight (kg) divided by height-squared (m^2). Daily dietary intake of phosphorus (mg), protein (g), energy (kcal), fiber (g), potassium (mg), and sodium (mg) were measured by analysis of the 3-day diet record. Phosphorus was analyzed in relation to energy (per 1000 kcal) and protein intake (per grams of total protein and per grams of plant protein). To further understand the type of protein intake within the cohort, plant-protein-to-total-protein ratio was analyzed. The *Nutrient Data System for Research* was used to assess the nutritional content of the recorded food items.

Statistical Methods

Participants' baseline characteristics were summarized using means ± standard deviations (SDs), medians ± interquartile range, and proportions according to race/ethnic category (non-Hispanic White, Black, Hispanic, and others). In primary analyses, we conducted logistic regression analyses examining the association of sociodemographic, comorbidity, dialysis treatment, health insurance, and dietary intake characteristics with likelihood of above median dietary intakes of phosphorus-to-total-protein ratio, phosphorus-to-plant-protein ratio, phosphorus/1000 kcal, and plant-protein-to-total-protein ratio, respectively. Three incremental levels of covariate adjustment were used:

(1) *Unadjusted model:* No covariate adjustment;

(2) *Case-mix model:* Covariates in the unadjusted model, as well as age, sex, race/ethnicity (Non-Hispanic White vs. Hispanic, Black, and other races/ethnicities, respectively), and diabetes;

(3) Expanded case-mix model: Covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber.

Distribution of nutrients overall and according to subgroups was summarized in figures and tables. BMI was the only covariate with missing data (N=9, 11%), and multiple imputation was used to account for these missing values. Analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Study Population

Among 80 hemodialysis patients who completed a 3-day diet record with interview, the mean ± SD age was 56 ± 18, of whom 41% were female, 18% were non-Hispanic White, 25% were Black, 36% were Hispanic, and 51% had diabetes (Table 2.1). Patients had a mean ± SD vintage of 6.4 ± 4.5 years and mean ± SD BMI of 28.5 ± 6.4.

Cohort Characteristics Associated with Dietary Intake

Analyses of predictors of nutrient intakes are shown in Tables 2.2a – 2.2d. A predictor of high intake of phosphorus-to-plant-protein ratio was Black race in the unadjusted (p=0.042) and case-mix model (p=0.048), and female sex in the unadjusted (p=0.014) expanded case-mix adjusted model (p=0.040), while a predictor of intake of low phosphorus-to-plant-protein ratio was older age (p=0.039) in the unadjusted model (Table 2B). Female sex was a predictor of high phosphorus/1000 kcal in both the unadjusted (p=0.0139), case-mix (p=0.017) and expanded case-mix adjusted model (p=0.042) (Table 2C). Predictors of low intake of plant-protein-to-total-protein ratio were female sex in the unadjusted (p=0.014), case-mix (p=0.046), and expanded case-mix adjusted models (p=0.026), Black race in the expanded case-mix model (p=0.044), and being single in the unadjusted (p=0.018) and case-mix model (p=0.018) (Table 2D). Analyses of predictors of dietary intakes of phosphorus-to-animal-protein ratio, animal-protein-to-plant-protein ratio, and animal-protein-to-total-protein ratio can be found in Supplemental Tables 2.1a through 2.1c.

Distribution of Dietary Intake across Clinically Relevant Subgroups

Figures 2.1a through 2.1d show the distributions of dietary intakes in the overall cohort and across subgroups, including age, sex, and race/ethnic group. When compared to patients less than 55 years old, patients who were at least 55 years old had lower phosphorus-to-total-protein ratio, lower phosphorus-to-plant-protein ratio, lower phosphorus/1000 kcal, and higher plant-protein-to-total-protein ratio. Moreover, compared to males, females had similar phosphorus-to-total-protein ratio, higher phosphorus-to-plant-protein ratio, higher phosphorus/1000 kcal, and lower plant-protein-to-total-protein ratio. Furthermore, Non-Hispanic Whites had the greatest dietary intakes of plant-protein-to-total-protein ratio when compared to all other race/ethnic groups. Blacks had the highest dietary intakes of phosphorus-to-plant-protein ratio, and Hispanics had the greatest dietary intakes of phosphorus/1000 kcal and phosphorus-to-total-protein ratio. Distributions of dietary intakes of phosphorus-to-animal-protein ratio, animal-protein-to-plant-protein ratio, and animal-protein-to-total-protein ratio can be found in Supplemental Figures 2.1a through 2.1c. Corresponding values of all dietary intakes can be found in Supplemental Table 2.2.

Discussion

Among a diverse cohort of dialysis patients, we observed that race, sex, age, and marital status were predictors of various measures of dietary phosphorus and protein intake. Black race was a predictor of higher phosphorus-to-plant-protein ratio and lower plant-protein-to-total-protein ratio, older age was a predictor of lower phosphorus-to-plant-protein ratio, female sex was a predictor of higher phosphorus-to-plant-protein ratio, phosphorus/1000 kcal, and low plant-protein-to-total-protein ratio, while being single was a predictor of low plant-protein-to-total-protein ratio. Analyses also showed differences in dietary phosphorus and plant protein intake in subgroups of age, sex, and race/ethnicity.

While there are significant consequences of serum phosphorus on mortality in dialysis patients, limited studies have directly assessed dietary intakes of phosphorus and protein and their associations with relevant patient characteristics. St-Jules et al. conducted an analysis of 140 White and African American dialysis patients who completed three 24-hour dietary recall questionnaires.[93] Their results suggested that African American race was associated with dietary phosphorus density (phosphorus/1000 kcal), older age was associated with dietary phosphorus density only in unadjusted analyses, and they did not find any significant relationship between sex and dietary phosphorus intake.

Given the evidence of differences in rates of mortality of dialysis patients within certain subgroups, such as age, sex, and race/ethnicity, we were not surprised to find differences of dietary intake within these subgroups as well.[46,94,95] In our study, Blacks and Hispanics had higher intakes of several measures of dietary phosphorus and lower intakes of plant protein, and Black race was a predictor of high phosphorus-to-plant-protein ratio. These intakes may be seen as undesirable based on current renal dietary recommendations, yet certain subpopulations of

Blacks and Hispanics tend to have higher rates of survival compared to non-Hispanic Whites.[46,96,97] The heterogeneity of dietary behaviors within this cohort highlights the importance of thorough assessments of patients' diets and subsequent individualized nutrition recommendations.

An advantage of our study was that dietary intake was directly assessed through 3-day diet records with interviews by a registered dietitian. Another strength of our study was that through analysis of foods with the Nutrition Data System for Research, we were able to distinguish dietary intake of plant versus animal protein. An additional strength was racial and ethnic diversity of the patient cohort. Several limitations of our study should be noted. First, a weakness of dietary assessment methods, including 3-day diet records, is that they tend to underestimate intake of calories and other nutrients.[55] We compensated for this limitation by using relative values instead of absolute values of nutrient intakes. Second, since these diet records were collected at a single point in time, we were not able to account for any seasonal variations in dietary behaviors. Third, our results may not be generalizable to the greater dialysis patient population. And fourth, selection bias may have occurred if the patients who declined to participate in our study had different dietary habits than those who did participate.

In conclusion, we found Black race, female sex, age, and marital status to be predictors of dietary intakes of phosphorus and plant protein intake. We also saw differences of dietary intakes of phosphorus and plant protein within subgroups of age, sex, and race/ethnicity. Follow up studies within this cohort should analyze associations between dietary intakes of phosphorus and protein with outcomes such as serum phosphorus, serum albumin, and mortality.

Table 2.1 Baseline characteristics of MADRAD hemodialysis patients according to race/ethnicity (N=80).

	Overall	Non-Hispanic White	Black	Hispanic	Other
N (%)	80	14 (18%)	20 (25%)	29 (36%)	17 (21%)
Age (mean ± SD)	56 ± 15	59 ± 12	63 ± 11	46 ± 15	64 ± 12
Female (%)	41	36	60	41	24
Vintage (years, mean ± SD)	6.4 ± 4.5	4.2 ± 2.1	8.0 ± 6.3	6.7 ± 4.3	5.8 ± 2.9
BMI (mean ± SD)	28.5 ± 6.4	29.1 ± 7.2	28.7 ± 6.7	30.0 ± 5.9	25.2 ± 5.2
Insurance (%)					
Medicare/Medicaid	79	93	65	79	82
Private	14	7	25	10	12
Other/Unknown	8	0	10	10	6
Dialysis Access					
AV Fistula/Graft	91	100	90	86	94
Catheter	4	0	0	7	6
Unknown	5	0	10	7	0
Marital Status (%)					
Married	36	14	35	31	65
Single	45	43	40	62	24
Other	19	43	25	7	12
COMORBIDITIES					
Diabetes (%)	51	43	40	55	65
CHF (%)	3	7	0	0	6
CAD (%)	3	0	0	3	6
Combined CV disease (%)	5	7	0	3	12
DIETARY INTAKE, median (IQR)					

Phosphorus/1000 kcal (mg/kcal)	596 (513, 672)	596 (523, 702)	581 (509, 649)	599 (504, 676)	588 (514, 654)
Total protein/1000 kcal (mg/kcal)	48.1 (38.3, 58.0)	48.5 (38.4, 54.4)	50.9 (42.6, 59.9)	43.8 (37.0, 58.0)	48.2 (38.7, 52.3)
Phosphorus-to-total-protein ratio (mg/g)	12.9 (10.6, 14.3)	13.4 (10.7, 15.0)	11.3 (10.0, 13.4)	13.5 (12.1, 14.7)	12.9 (10.7, 17.5)
Phosphorus-to-plant-protein ratio (mg/g)	47.8 (37.8, 61.0)	41.1 (34.8, 59.8)	53.7 (42.8, 64.3)	50.1 (40.8, 65.6)	41.3 (30.4, 59.1)
Phosphorus-to-animal-protein ratio (mg/g)	16.7 (14.2, 22.2)	18.8 (14.7, 22.2)	15.0 (12.7, 17.5)	18.1 (14.3, 23.0)	16.6 (15.4, 26.7)
Plant-protein-to-total-protein ratio (g)	0.28 (0.19, 0.34)	0.32 (0.22, 0.38)	0.24 (0.16, 0.29)	0.28 (0.21, 0.34)	0.30 (0.28, 0.37)
Animal-protein-to-total-protein ratio (g)	0.72 (0.66, 0.81)	0.68 (0.62, 0.78)	0.76 (0.71, 0.84)	0.72 (0.66, 0.79)	0.70 (0.63, 0.72)
Animal-protein-to-plant-protein (g)	2.6 (2.0, 4.2)	2.1 (1.6, 3.5)	3.2 (2.5, 5.1)	2.6 (2.0, 3.8)	2.4 (1.7, 2.6)
K/1000 kcal (mg/kcal)	1076 (891, 1282)	957 (909, 1117)	1093 (806, 1223)	1046 (887, 1230)	1287 (1085, 1510)
Fiber/1000 kcal (g/kcal)	7.7 (6.0, 9.3)	7.6 (5.9, 8.2)	6.5 (5.5, 8.4)	8.0 (6.5, 8.6)	8.6 (6.8, 12.9)

MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study; BMI, body mass index; CHF, congestive heart failure; CAD, coronary artery disease; CV, cardiovascular

Table 2.2a. Logistic regression analyses of predictors of phosphorus-to-total-protein ratio greater than median value of 12.9 mg/g (reference: ≤ 12.9 mg/g) among MADRAD hemodialysis patients (N = 80).

	Unadjusted				Case-mix				Expanded case-mix			
	P value	OR	95% CI		P value	OR	95% CI		P value	OR	95% CI	
Age (Δ10)	0.2663	0.842	0.622	1.140	0.3963	0.850	0.583	1.238	0.5569	0.853	0.502	1.450
Female (vs. Male)	0.8204	0.902	0.370	2.198	0.9098	1.058	0.402	2.784	0.6587	1.281	0.426	3.850
Race/ethnicity (vs. Non-Hispanic White)												
Black	0.0528	0.238	0.056	1.018	0.0648	0.246	0.055	1.090	0.0706	0.189	0.031	1.151
Hispanic	0.5712	0.684	0.183	2.548	0.3760	0.521	0.123	2.209	0.2948	0.425	0.086	2.108
Other	0.5252	0.625	0.147	2.664	0.5431	0.630	0.142	2.789	0.5644	0.605	0.109	3.344
Diabetes	0.5026	1.351	0.561	3.254	0.5117	1.371	0.535	3.514	0.4477	1.577	0.486	5.116
Vintage (Δ1-year)	0.7051	0.981	0.889	1.083	0.6432	1.027	0.917	1.150	0.4039	1.060	0.925	1.215
Access (vs. AVF/AVG)												
Catheter	0.9751	-	-	-	0.9752	-	-	-	0.9760	-	-	-
Unknown	0.9362	1.086	0.145	8.128	0.8465	1.244	0.136	11.400	0.8213	1.347	0.102	17.871
BMI (Δ5)	0.8475	1.037	0.717	1.499	0.9551	0.987	0.626	1.555	0.9969	0.999	0.593	1.682

Insurance status (vs. Medicare/MediCal)												
Private	0.3814	0.554	0.147	2.081	0.5554	0.643	0.148	2.788	0.9959	1.004	0.189	5.337
Other	0.4634	1.937	0.331	11.348	0.3396	2.543	0.374	17.283	0.4098	2.558	0.274	23.866
Marital status (vs. married)												
Single	0.9326	0.959	0.360	2.552	0.4952	0.669	0.211	2.125	0.8011	0.839	0.214	3.293
Other	0.4619	1.607	0.454	5.688	0.3820	1.889	0.454	7.862	0.3646	2.094	0.424	10.351
Dietary fiber (Δ1)	0.0280*	1.124	1.013	1.246	0.0564	1.112	0.997	1.240	0.1486	1.090	0.970	1.226

Case-mix analyses adjusted for age, sex, race/ethnicity, and diabetes. Expanded case-mix analyses adjusted for covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber. AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.
* Indicates p-value < 0.05

Table 2.2b. Logistic regression analyses of predictors of phosphorus-to-plant-protein ratio greater than median value of 47.8 mg/g (reference: ≤ 47.8 mg/g) among MADRAD hemodialysis patients (N = 80).

	Unadjusted				**Case-mix**				**Expanded case-mix**			
	P value	**OR**	**95% CI**		**P value**	**OR**	**95% CI**		**P value**	**OR**	**95% CI**	
Age (Δ10)	0.0389*	0.714	0.519	0.983	0.0705	0.685	0.454	1.032	0.0904	0.620	0.356	1.078
Female (vs. Male)	0.0139*	3.222	1.268	8.187	0.0607	2.637	0.957	7.262	0.0402*	3.483	1.057	11.479
Race/ethnicity (vs. Non-Hispanic White)												
Black	0.0420*	4.643	1.057	20.385	0.0477*	5.053	1.016	25.124	0.0999	4.807	0.741	31.201
Hispanic	0.0715	3.542	0.895	14.007	0.2935	2.271	0.491	10.497	0.2787	2.636	0.456	15.221
Other	0.6907	1.364	0.296	6.283	0.4607	1.856	0.359	9.602	0.3371	2.591	0.371	18.100
Diabetes	0.8231	1.105	0.460	2.657	0.4831	1.430	0.526	3.890	0.5090	1.519	0.439	5.255
Vintage (Δ1-year)	0.7055	1.019	0.923	1.125	0.9512	1.004	0.892	1.130	0.5029	1.051	0.909	1.214
Access (vs. AVF/AVG)												
Catheter	0.5634	0.487	0.042	5.604	0.6373	0.536	0.040	7.165	0.5940	0.430	0.019	9.587
Unknown	0.9787	0.973	0.130	7.283	0.1601	0.192	0.019	1.919	0.2910	0.236	0.016	3.452
BMI (Δ5)	0.2293	1.261	0.864	1.841	0.8386	1.057	0.617	1.811	0.9895	1.004	0.548	1.840

Insurance status (vs. Medicare/MediCal)												
Private	0.2470	2.187	0.581	8.231	0.9516	1.051	0.210	5.264	0.9785	0.975	0.160	5.948
Other	0.1032	6.249	0.690	56.605	0.1360	5.958	0.570	62.254	0.1577	6.416	0.487	84.559
Marital status (vs. married)												
Single	0.1159	2.226	0.821	6.037	0.3819	1.709	0.514	5.685	0.5538	1.529	0.375	6.231
Other	0.9297	0.944	0.265	3.363	0.7597	1.261	0.286	5.561	0.5123	1.788	0.314	10.168
Dietary fiber (Δ1)	0.2441	0.945	0.859	1.039	0.1324	0.920	0.825	1.026	0.1917	0.919	0.811	1.043

Case-mix analyses adjusted for age, sex, race/ethnicity, and diabetes. Expanded case-mix analyses adjusted for covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber. AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.
* Indicates p-value < 0.05

Table 2.2c. Logistic regression analyses of predictors of phosphorus/1000 kcal greater than median value of 596 mg/kcal (reference: ≤ 596 mg/kcal) among MADRAD hemodialysis patients (N = 80).

	Unadjusted				Case-mix				Expanded case-mix			
	P value	**OR**	**95% CI**		**P value**	**OR**	**95% CI**		**P value**	**OR**	**95% CI**	
Age (Δ10)	0.2538	0.838	0.619	1.135	0.3652	0.837	0.569	1.230	0.4830	0.824	0.480	1.415
Female (vs. Male)	0.0139*	3.222	1.268	8.187	0.0171*	3.312	1.237	8.866	0.0417*	3.322	1.046	10.548
Race (vs. Non-Hispanic White)												
Black	>0.999	1.000	0.255	3.919	0.7444	0.783	0.181	3.397	0.7916	0.787	0.133	4.658
Hispanic	0.9156	1.071	0.299	3.838	0.7561	0.795	0.186	3.390	0.8876	0.886	0.165	4.756
Other	0.8706	0.889	0.216	3.663	0.8801	1.123	0.250	5.041	0.9150	1.100	0.191	6.341
Diabetes	0.8231	0.905	0.376	2.175	0.9576	0.975	0.378	2.512	0.3084	0.530	0.156	1.799
Vintage (Δ1-year)	0.3662	0.954	0.862	1.056	0.3004	0.941	0.839	1.056	0.1950	0.908	0.785	1.051
Access (vs. AVF/AVG)												
Catheter	0.5934	0.514	0.045	5.919	0.8057	0.729	0.059	9.053	0.7200	1.687	0.097	29.490
Unknown	0.3392	3.083	0.306	31.038	0.6273	1.854	0.153	22.405	0.3703	4.523	0.166	123.315
BMI (Δ5)	0.2937	1.223	0.840	1.779	0.3570	1.240	0.784	1.962	0.3961	1.260	0.739	2.148

Insurance status (vs. Medicare/MediCal)												
Private	0.1610	2.753	0.668	11.341	0.4722	1.765	0.375	8.315	0.9528	0.947	0.154	5.820
Other	0.1605	0.206	0.023	1.869	0.1509	0.173	0.016	1.894	0.0774	0.104	0.008	1.282
Marital status (vs. married)												
Single	0.7581	1.167	0.437	3.112	0.9521	0.965	0.305	3.060	0.3500	0.509	0.124	2.097
Other	0.2496	0.467	0.128	1.708	0.2160	0.397	0.092	1.715	0.0606	0.190	0.033	1.077
Dietary fiber (Δ1)	0.1375	0.929	0.843	1.024	0.0819	0.910	0.818	1.012	0.0650	0.892	0.789	1.007

Case-mix analyses adjusted for age, sex, race/ethnicity, and diabetes. Expanded case-mix analyses adjusted for covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber. AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.
* Indicates p-value < 0.05

Table 2.2d. Logistic regression analyses of predictors of plant-protein-to-total-protein ratio greater than median value of 0.3 g (reference: ≤ 0.3 g) among MADRAD hemodialysis patients (N = 80).

	Unadjusted				Case-mix				Expanded case-mix			
	P value	**OR**	**95% CI**		**P value**	**OR**	**95% CI**		**P value**	**OR**	**95% CI**	
Age (Δ10)	0.9397	1.012	0.752	1.361	0.7831	0.948	0.646	1.390	0.7647	0.915	0.513	1.634
Female (vs. Male)	0.0139*	0.310	0.122	0.789	0.0464*	0.368	0.138	0.984	0.0264*	0.229	0.062	0.841
Race/ethnicity (vs. Non-Hispanic White)												
Black	0.1189	0.321	0.077	1.339	0.2124	0.388	0.088	1.718	0.0440*	0.121	0.015	0.945
Hispanic	0.5864	0.700	0.194	2.530	0.6256	0.700	0.167	2.932	0.1067	0.224	0.036	1.380
Other	0.4383	1.800	0.407	7.957	0.4647	1.785	0.378	8.441	0.5190	0.525	0.074	3.727
Diabetes	0.8231	0.905	0.376	2.175	0.5451	0.740	0.280	1.960	0.8209	1.165	0.311	4.363
Vintage (Δ1-year)	0.9268	0.995	0.902	1.099	0.6508	1.027	0.914	1.155	0.4824	1.057	0.905	1.235
Access (vs. AVF/AVG)												
Catheter	0.9752	-	-	-	0.9756	-	-	-	0.9745	-	-	-
Unknown	0.3632	0.343	0.034	3.449	0.5873	0.489	0.037	6.467	0.7541	0.594	0.023	15.472
BMI (Δ5)	0.1481	0.754	0.514	1.106	0.3180	0.775	0.469	1.279	0.4326	0.783	0.425	1.443

Insurance status (vs. Medicare/MediCal)												
Private	0.6721	1.320	0.365	4.775	0.1389	3.393	0.673	17.107	0.0616	7.381	0.907	60.031
Other	0.3821	2.200	0.375	12.887	0.3740	2.440	0.341	17.429	0.4824	2.298	0.226	23.411
Marital status (vs. married)												
Single	0.0177*	0.286	0.102	0.805	0.0180*	0.215	0.060	0.768	0.1583	0.358	0.086	1.492
Other	0.0692	0.300	0.082	1.099	0.0755	0.249	0.054	1.154	0.1090	0.233	0.039	1.384
Dietary fiber (g) (Δ1)	0.0479*	1.108	1.001	1.226	0.0583	1.119	0.996	1.256	0.0690	1.140	0.990	1.312

Case-mix analyses adjusted for age, sex, race/ethnicity, and diabetes. Expanded case-mix analyses adjusted for covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber. AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.
* Indicates p-value < 0.05

Figure 2.1a. Among 80 hemodialysis patients in the MADRAD study with diet records, distribution of dietary phosphorus-to-total-protein ratio (mg/g) in the overall cohort, <55 years old vs. ≥ 55 years old, male vs. female, and non-Hispanic White vs. Black vs. Hispanic vs. others, respectively.

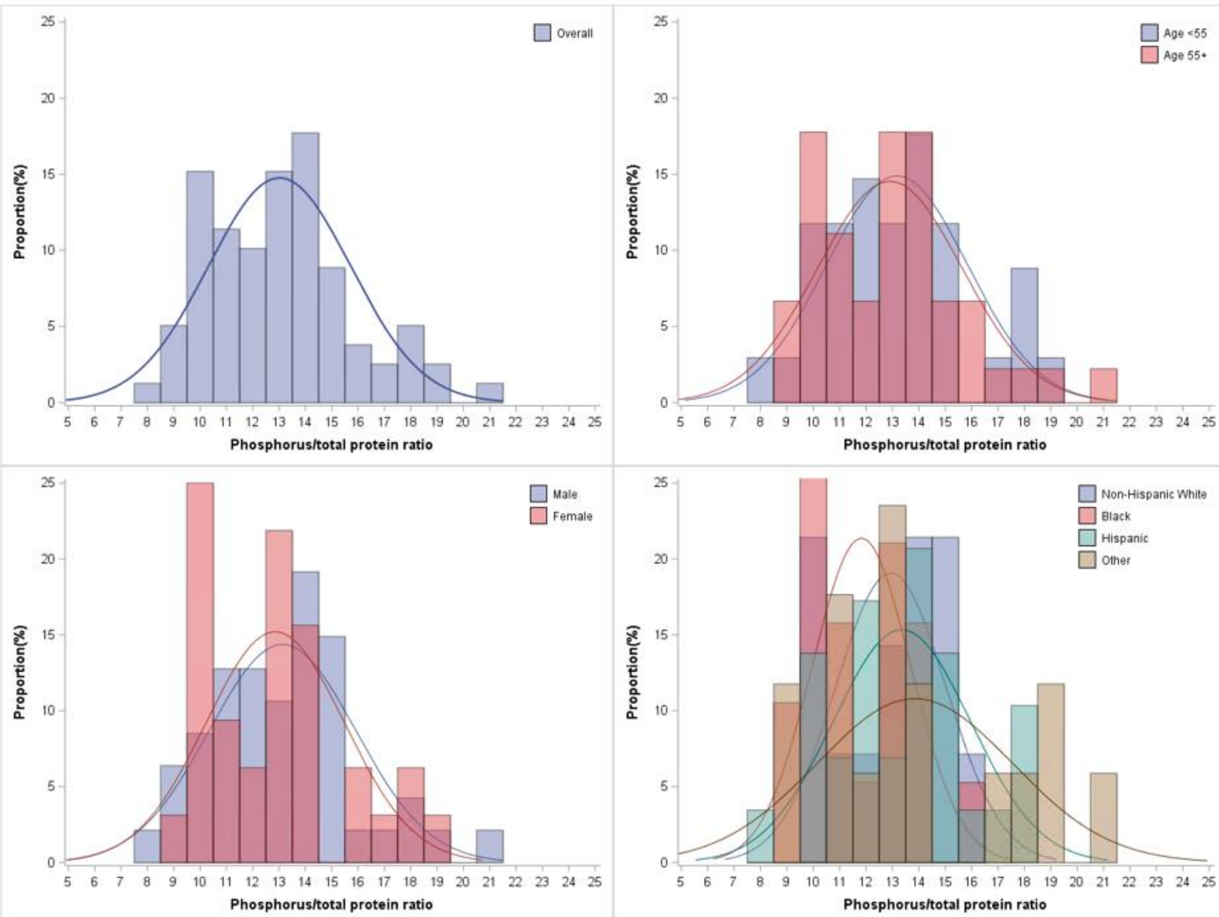


Figure 2.1b. Among 80 hemodialysis patients in the MADRAD study with diet records, distribution of dietary phosphorus-to-plant-protein ratio (mg/g) in the overall cohort, <55 years old vs. ≥ 55 years old, male vs. female, and non-Hispanic White vs. Black vs. Hispanic vs. others, respectively.

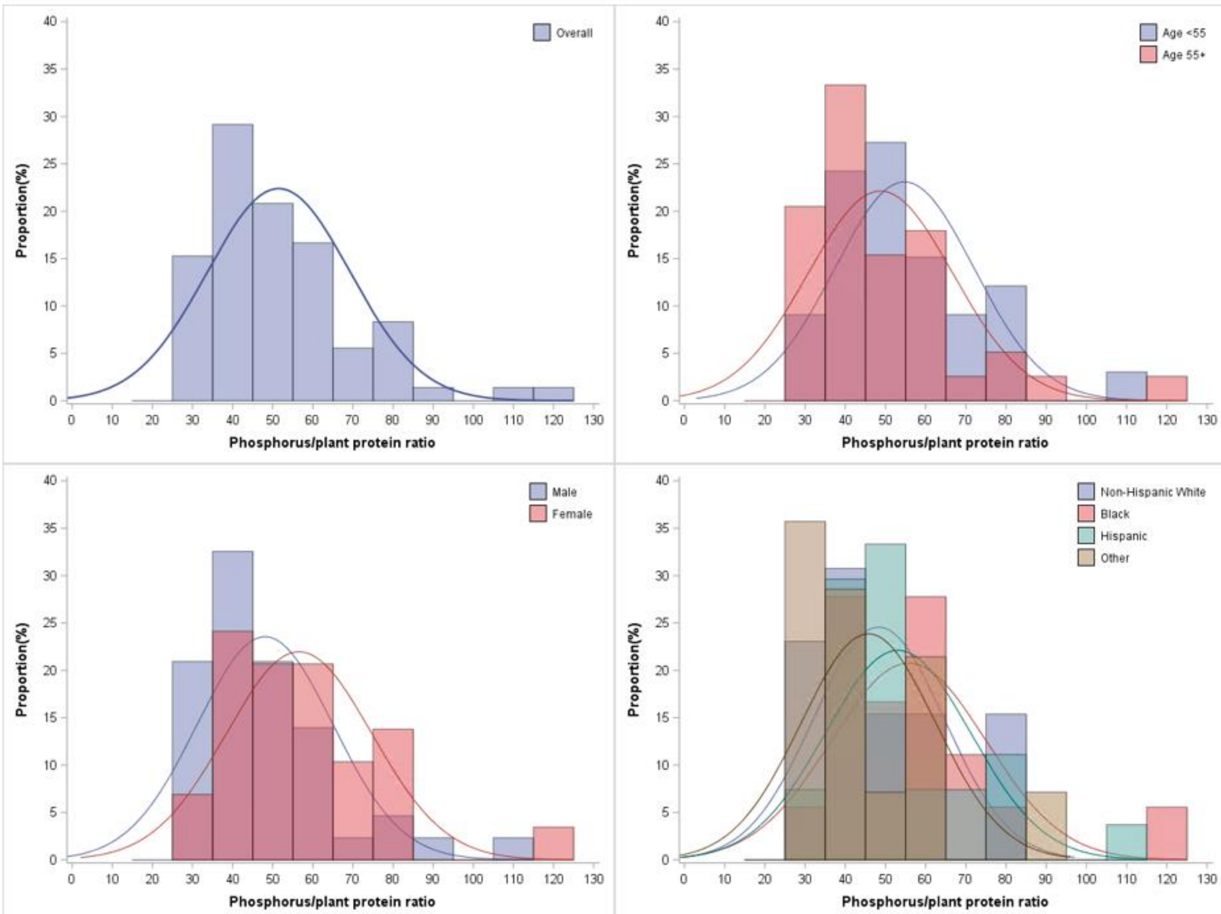


Figure 2.1c. Among 80 hemodialysis patients in the MADRAD study with diet records, distribution of dietary phosphorus/1000 kcal (mg/kcal) in the overall cohort, <55 years old vs. ≥ 55 years old, male vs. female, and non-Hispanic white vs. Black vs. Hispanic vs. others, respectively.

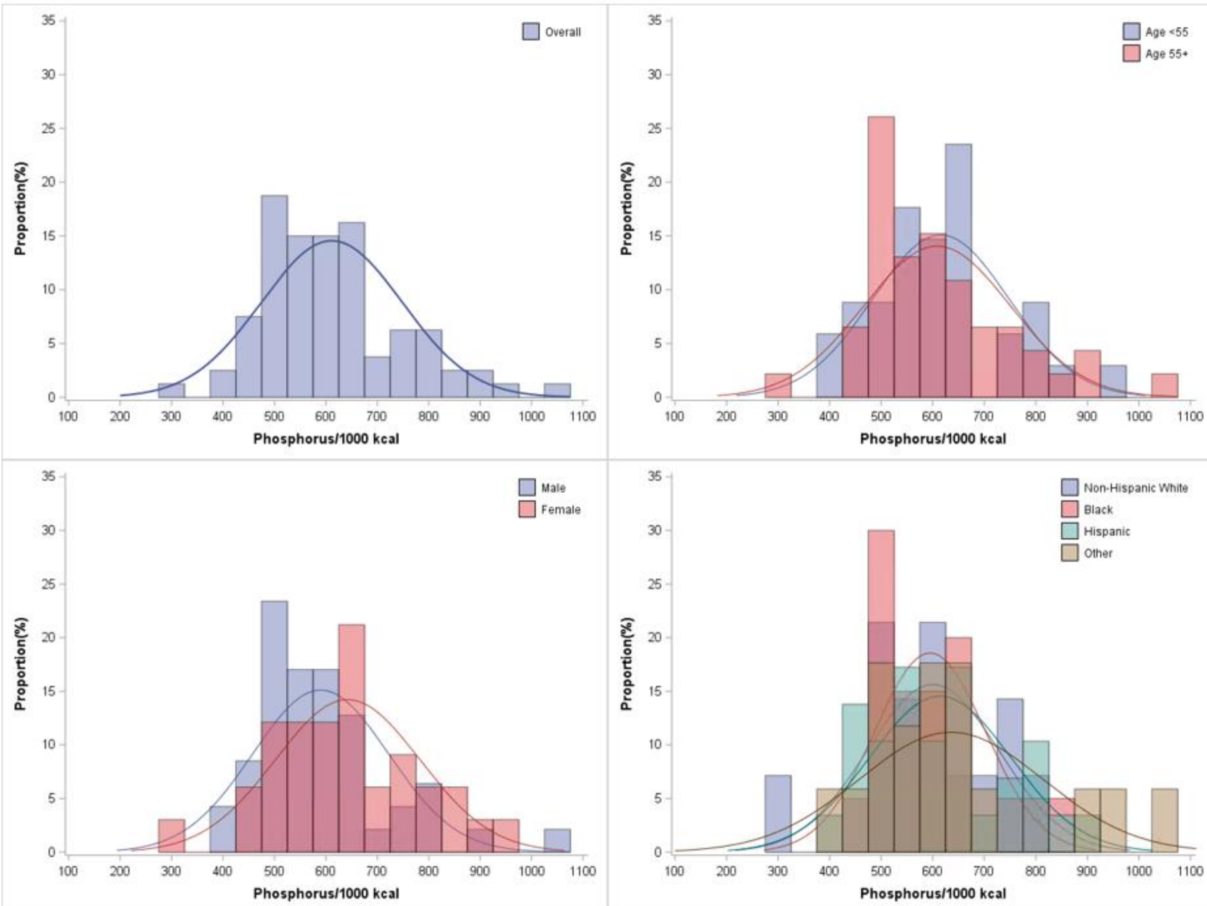
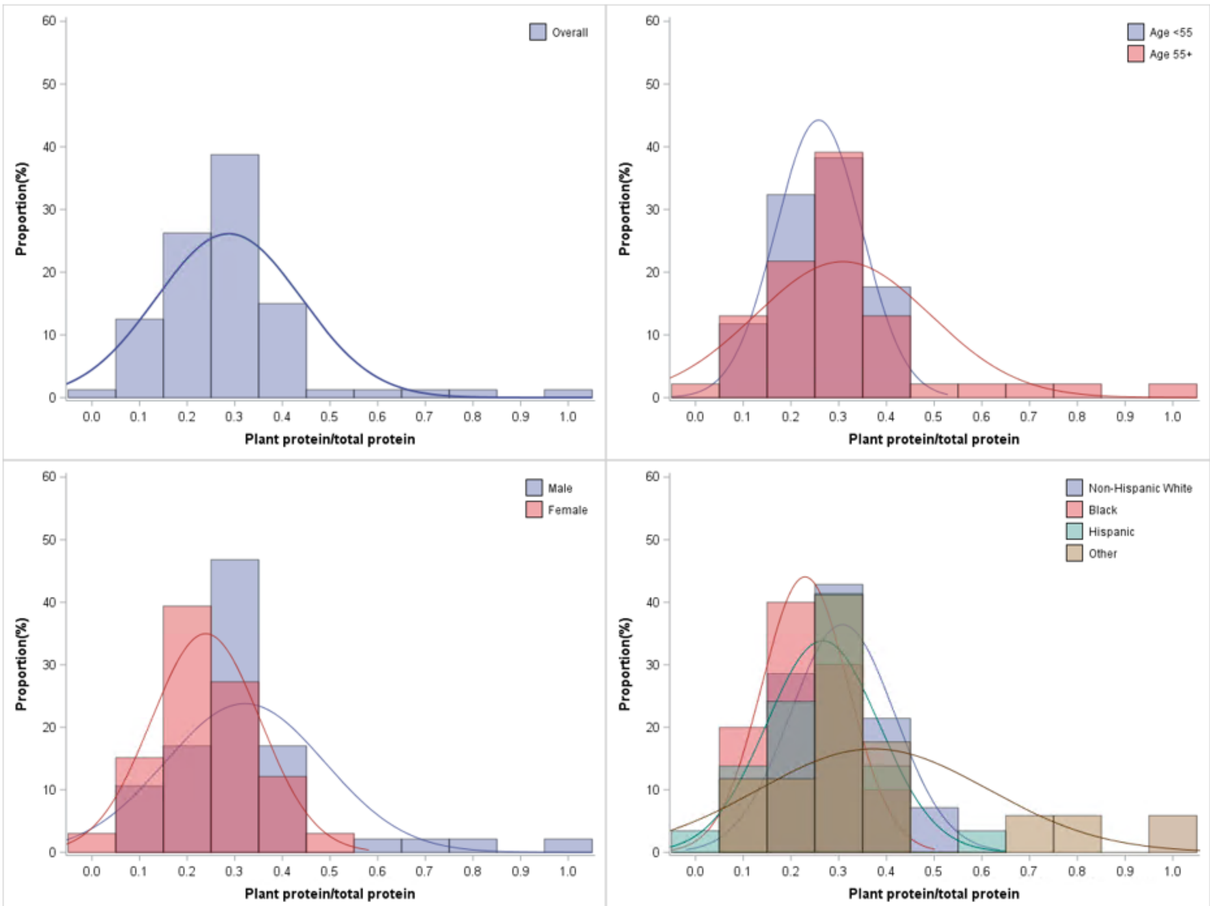


Figure 2.1d. Among 80 hemodialysis patients in the MADRAD study with diet records, distribution of dietary plant-protein-to-total-protein ratio (mg/g) in the overall cohort, <55 years old vs. ≥ 55 years old, male vs. female, and non-Hispanic White vs. Black vs. Hispanic vs. others, respectively.



Supplemental Table 2.1a. Logistic regression analyses of predictors of phosphorus-to-animal-protein ratio greater than median value of 16.7 mg/g (reference: ≤ 16.7 mg/g) among MADRAD hemodialysis patients (N = 80).

	Unadjusted				Case-mix				Expanded case-mix			
	P value	OR	95% CI		P value	OR	95% CI		P value	OR	95% CI	
Age (Δ10)	0.2663	0.842	0.622	1.140	0.5179	0.884	0.609	1.284	0.8540	0.947	0.530	1.692
Female (vs. Male)	0.2576	0.595	0.242	1.462	0.3076	0.608	0.234	1.581	0.4659	0.633	0.186	2.161
Race/ethnicity (vs. Non-Hispanic White)												
Black	0.2049	0.404	0.099	1.641	0.3032	0.471	0.112	1.975	0.1968	0.270	0.037	1.971
Hispanic	0.9267	1.062	0.292	3.863	0.9026	0.916	0.225	3.733	0.5193	0.560	0.096	3.261
Other	0.5768	0.667	0.161	2.769	0.5618	0.649	0.150	2.799	0.2859	0.348	0.050	2.419
Diabetes	0.8231	1.105	0.460	2.657	0.8458	1.097	0.433	2.781	0.6585	1.339	0.367	4.895
Vintage (Δ1-year)	0.8428	0.990	0.897	1.093	0.7778	1.016	0.908	1.137	0.6951	1.031	0.885	1.201
Access (vs. AVF/AVG)												
Catheter	0.9751	-	-	-	0.9755	-	-	-	0.9776	-	-	-
Unknown	0.9362	1.086	0.145	8.128	0.8909	1.170	0.125	10.953	0.7798	1.481	0.095	23.174
BMI (Δ5)	0.8268	0.960	0.663	1.388	0.6155	0.889	0.562	1.407	0.5987	0.850	0.464	1.557

Insurance status (vs. Medicare/MediCal)												
Private	0.4346	0.590	0.157	2.217	0.7783	0.812	0.190	3.474	0.5412	1.762	0.286	10.853
Other	0.1443	5.160	0.570	46.713	0.1487	5.505	0.544	55.730	0.1396	7.590	0.516	111.699
Marital status (vs. married)												
Single	0.1763	0.504	0.187	1.360	0.0357*	0.268	0.078	0.916	0.3031	0.449	0.098	2.062
Other	0.7373	0.807	0.230	2.830	0.7882	0.823	0.198	3.413	0.8576	0.846	0.137	5.237
Dietary fiber (g) (Δ1)	0.0001*	1.308	1.139	1.502	0.0003*	1.304	1.128	1.507	0.0011*	1.295	1.109	1.512

Case-mix analyses adjusted for age, sex, race/ethnicity, and diabetes. Expanded case-mix analyses adjusted for covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber. AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.
* Indicates p-value < 0.05

Supplemental Table 2.1b. Logistic regression analyses of predictors of animal-protein-to-plant-protein ratio greater than median value of 2.6 g (reference: ≤ 2.6 g) among MADRAD hemodialysis patients (N = 80).

	Unadjusted				Case-mix				Expanded case-mix			
	P value	**OR**	**95% CI**		**P value**	**OR**	**95% CI**		**P value**	**OR**	**95% CI**	
Age (Δ10)	0.9397	0.989	0.735	1.330	0.7831	1.055	0.719	1.548	0.7647	1.093	0.612	1.951
Female (vs. Male)	0.0139*	3.222	1.268	8.187	0.0464*	2.718	1.016	7.271	0.0264*	4.368	1.189	16.050
Race/ethnicity (vs. Non-Hispanic White)												
Black	0.1189	3.111	0.747	12.956	0.2124	2.578	0.582	11.416	0.0440*	8.270	1.058	64.631
Hispanic	0.5864	1.429	0.395	5.163	0.6256	1.428	0.341	5.983	0.1067	4.465	0.725	27.506
Other	0.4383	0.556	0.126	2.456	0.4647	0.560	0.118	2.649	0.5190	1.906	0.268	13.543
Diabetes	0.8231	1.105	0.460	2.657	0.5451	1.350	0.510	3.574	0.8209	0.859	0.229	3.216
Vintage (Δ1-year)	0.9268	1.005	0.910	1.109	0.6508	0.973	0.865	1.094	0.4824	0.946	0.810	1.105
Access (vs. AVF/AVG)												
Catheter	0.9752	-	-	-	0.9756	-	-	-	0.9745	-	-	-
Unknown	0.3632	2.919	0.290	29.383	0.5873	2.044	0.155	27.022	0.7541	1.683	0.065	43.807
BMI (Δ5)	0.1481	1.327	0.905	1.946	0.3180	1.291	0.782	2.131	0.4326	1.277	0.693	2.354

Insurance status (vs. Medicare/MediCal)												
Private	0.6721	0.758	0.209	2.740	0.1389	0.295	0.058	1.486	0.0616	0.135	0.017	1.102
Other	0.3821	0.455	0.078	2.663	0.3740	0.410	0.057	2.928	0.4824	0.435	0.043	4.434
Marital status (vs. married)												
Single	0.0177*	3.492	1.242	9.815	0.0180*	4.652	1.301	16.632	0.1583	2.796	0.670	11.662
Other	0.0692	3.333	0.910	12.212	0.0755	4.023	0.867	18.669	0.1090	4.299	0.723	25.578
Dietary fiber (Δ1)	0.0479*	0.903	0.815	0.999	0.0583	0.894	0.796	1.004	0.0690	0.878	0.762	1.010

Case-mix analyses adjusted for age, sex, race/ethnicity, and diabetes. Expanded case-mix analyses adjusted for covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber. AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.
* Indicates p-value < 0.05

Supplemental Table 2.1c. Logistic regression analyses of predictors of animal-protein-to-total-protein ratio greater than median value of 0.7 g (reference: ≤ 0.7 g) among MADRAD hemodialysis patients (N = 80).

	Unadjusted				Case-mix				Expanded case-mix			
	P value	**OR**	**95% CI**		**P value**	**OR**	**95% CI**		**P value**	**OR**	**95% CI**	
Age (Δ10)	0.9397	0.989	0.735	1.330	0.7831	1.055	0.719	1.548	0.7647	1.093	0.612	1.951
Female (vs. Male)	0.0139*	3.222	1.268	8.187	0.0464*	2.718	1.016	7.271	0.0264*	4.368	1.189	16.050
Race/ethnicity (vs. Non-Hispanic White)												
Black	0.1189	3.111	0.747	12.956	0.2124	2.578	0.582	11.416	0.0440*	8.270	1.058	64.631
Hispanic	0.5864	1.429	0.395	5.163	0.6256	1.428	0.341	5.983	0.1067	4.465	0.725	27.506
Other	0.4383	0.556	0.126	2.456	0.4647	0.560	0.118	2.649	0.5190	1.906	0.268	13.543
Diabetes	0.8231	1.105	0.460	2.657	0.5451	1.350	0.510	3.574	0.8209	0.859	0.229	3.216
Vintage (Δ1-year)	0.9268	1.005	0.910	1.109	0.6508	0.973	0.865	1.094	0.4824	0.946	0.810	1.105
Access (vs. AVF/AVG)												
Catheter	0.9752	-	-	-	0.9756	-	-	-	0.9745	-	-	-
Unknown	0.3632	2.919	0.290	29.383	0.5873	2.044	0.155	27.022	0.7541	1.683	0.065	43.807
BMI (Δ5)	0.1481	1.327	0.905	1.946	0.3180	1.291	0.782	2.131	0.4326	1.277	0.693	2.354

Insurance status (vs. Medicare/MediCal)												
Private	0.6721	0.758	0.209	2.740	0.1389	0.295	0.058	1.486	0.0616	0.135	0.017	1.102
Other	0.3821	0.455	0.078	2.663	0.3740	0.410	0.057	2.928	0.4824	0.435	0.043	4.434
Marital status (vs. married)												
Single	0.0177*	3.492	1.242	9.815	0.0180*	4.652	1.301	16.632	0.1583	2.796	0.670	11.662
Other	0.0692	3.333	0.910	12.212	0.0755	4.023	0.867	18.669	0.1090	4.299	0.723	25.578
Dietary fiber (Δ1)	0.0479*	0.903	0.815	0.999	0.0583	0.894	0.796	1.004	0.0690	0.878	0.762	1.010

Case-mix analyses adjusted for age, sex, race/ethnicity, and diabetes. Expanded case-mix analyses adjusted for covariates in the case-mix model, as well as vintage, access, BMI, insurance status, marital status, and dietary fiber. AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.
* Indicates p-value < 0.05

Supplemental Table 2.2. Distribution of dietary intakes across various subgroups among 80 hemodialysis patients in the MADRAD study.

Dietary phosphorus-to-total-protein ratio (mg/g)														
	N	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**0.50%**	**1%**	**5%**	**95%**	**99%**	**99.50%**
Overall	80	8.11	21.35	12.95	2.74	12.87	10.63	14.28	8.11	8.11	9.27	18.16	21.35	21.35
Age														
<55	34	8.48	18.69	13.17	2.68	12.93	11.07	14.61	8.48	8.48	8.84	18.25	18.69	18.69
55+	46	8.11	21.35	12.8	2.81	12.76	10.47	14.23	8.11	8.11	9.31	17.86	21.35	21.35
Gender														
Male	47	8.48	21.35	13.13	2.78	12.91	10.73	14.68	8.48	8.48	9.23	18.06	21.35	21.35
Female	33	8.11	18.69	12.71	2.71	12.84	10.47	13.64	8.11	8.11	9.31	18.25	18.69	18.69
Race/ethnicity														
Non-Hispanic White	14	9.65	15.69	12.93	2.09	13.42	10.73	15.04	9.65	9.65	9.65	15.69	15.69	15.69
Black	20	8.11	15.6	11.64	2	11.28	10.05	13.36	8.11	8.11	8.71	14.91	15.6	15.6
Hispanic	29	8.48	18.25	13.35	2.6	13.53	12.09	14.68	8.48	8.48	9.59	18.06	18.25	18.25
Other	17	8.84	21.35	13.84	3.7	12.91	10.67	17.45	8.84	8.84	8.84	21.35	21.35	21.35
Dietary phosphorus-to-animal-protein ratio (mg/g)														
	N	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**0.50%**	**1%**	**5%**	**95%**	**99%**	**99.50%**
Overall	80	9.45	5727.31	91.04	638.26	16.69	14.25	22.23	9.45	9.45	10.52	35.17	5727.31	5727.31
Age														
<55	34	9.45	29.63	18.26	5.32	16.64	14.06	21.59	9.45	9.45	11.43	27.16	29.63	29.63
55+	46	9.5	5727.31	144.84	841.54	16.98	14.39	22.26	9.5	9.5	10.12	58.75	5727.31	5727.31
Gender														
Male	47	9.45	5727.31	142.74	832.45	17.62	14.7	22.41	9.45	9.45	12.02	58.75	5727.31	5727.31
Female	33	9.5	29.95	17.41	5.82	16.43	13.08	21.38	9.5	9.5	9.66	29.63	29.95	29.95
Race/ethnicity														
Non-Hispanic White	14	12.04	29.95	19.37	5.45	18.82	14.7	22.19	12.04	12.04	12.04	29.95	29.95	29.95
Black	20	9.5	22.41	15.39	3.61	14.97	12.73	17.48	9.5	9.5	9.81	22.34	22.41	22.41
Hispanic	29	9.45	40.4	19.11	6.53	18.05	14.34	23.04	9.45	9.45	9.66	27.16	40.4	40.4

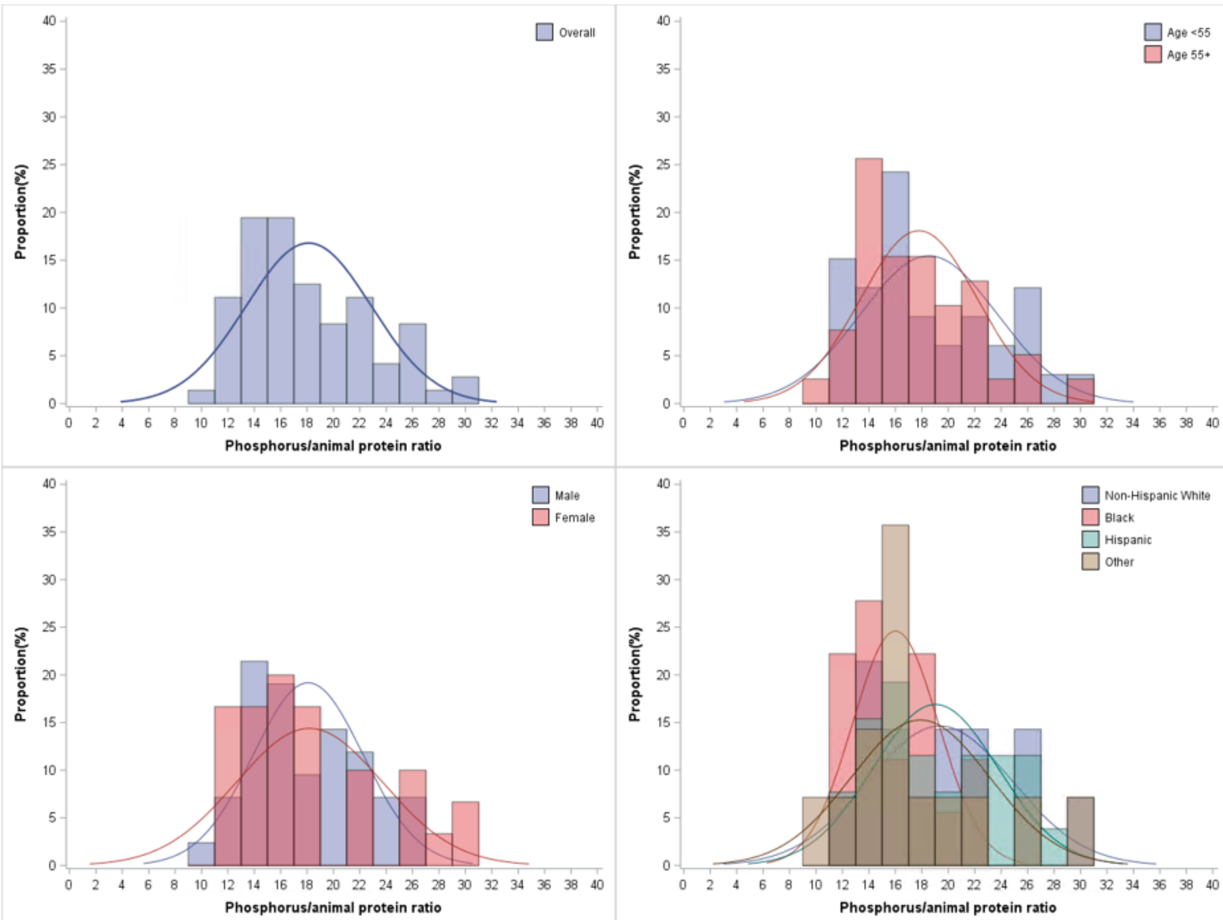
Other	17	10.93	5727.31	361.77	1382.89	16.62	15.36	26.71	10.93	10.93	10.93	5727.31	5727.31	5727.31
Dietary phosphorus-to-plant-protein ratio (mg/g)														
	N	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**0.50%**	**1%**	**5%**	**95%**	**99%**	**99.50%**
Overall	80	17.92	1186.66	68.3	129.81	47.8	37.81	60.96	17.92	17.92	25.04	124.21	1186.66	1186.66
Age														
<55	34	30.43	134.86	57.07	21.87	51.19	40.82	65.64	30.43	30.43	33.97	107.21	134.86	134.86
55+	46	17.92	1186.66	76.59	170.49	44.2	34.91	58.35	17.92	17.92	24.62	131.78	1186.66	1186.66
Gender														
Male	47	17.92	131.78	48.2	21.4	43.75	34.91	59.11	17.92	17.92	24.83	86.48	131.78	131.78
Female	33	24.62	1186.66	96.92	198.75	55.14	43.57	70.03	24.62	24.62	31.02	212.5	1186.66	1186.66
Race/ethnicity														
Non-Hispanic White	14	24.62	78.75	46.62	16.84	41.1	34.84	59.79	24.62	24.62	24.62	78.75	78.75	78.75
Black	20	24.34	212.5	62.02	40.43	53.65	42.78	64.28	24.34	24.34	27.68	164.57	212.5	212.5
Hispanic	29	25.26	1186.66	95.02	211.22	50.09	40.82	65.64	25.26	25.26	33.97	134.86	1186.66	1186.66
Other	17	17.92	131.78	47.94	27.58	41.29	30.43	59.11	17.92	17.92	17.92	131.78	131.78	131.78
Dietary phosphorus/1000 kcal (mg/kcal)														
	N	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**0.50%**	**1%**	**5%**	**95%**	**99%**	**99.50%**
Overall	80	319.93	1047.34	611.39	137.09	595.7	512.65	671.93	319.93	319.93	434.41	876.33	1047.34	1047.34
Age														
<55	34	405.64	953.43	615.56	132.19	606.28	525.02	666.04	405.64	405.64	408.54	865.22	953.43	953.43
55+	46	319.93	1047.34	608.31	141.96	580.01	511.73	676.23	319.93	319.93	435.45	887.45	1047.34	1047.34
Gender														
Male	47	405.64	1047.34	589.77	132	555.4	508.1	643.77	405.64	405.64	433.37	822.52	1047.34	1047.34
Female	33	319.93	953.43	642.18	140.3	633.66	552.73	739.55	319.93	319.93	447.29	887.45	953.43	953.43
Race/ethnicity														
Non-Hispanic White	14	319.93	797.19	600.3	127.56	596.47	522.56	702.39	319.93	319.93	319.93	797.19	797.19	797.19
Black	20	458.99	832.35	594.67	107.42	581.13	508.74	648.64	458.99	458.99	467.75	819.33	832.35	832.35
Hispanic	29	408.54	887.45	614.19	137.19	599.45	504.02	676.23	408.54	408.54	433.37	865.22	887.45	887.45
Other	17	405.64	1047.34	635.42	178.45	587.77	513.57	653.73	405.64	405.64	405.64	1047.34	1047.34	1047.34

Dietary animal-protein-to-plant-protein ratio (g)														
	N	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**0.50%**	**1%**	**5%**	**95%**	**99%**	**99.50%**
Overall	80	0	122.78	4.87	13.59	2.6	1.95	4.25	0	0	0.72	10.15	122.78	122.78
Age														
<55	34	1.4	11.8	3.57	2.28	2.72	1.96	4.76	1.4	1.4	1.54	8.78	11.8	11.8
55+	46	0	122.78	5.83	17.83	2.48	1.94	3.5	0	0	0.42	11.53	122.78	122.78
Gender														
Male	47	0	8.78	2.84	1.89	2.41	1.78	3.19	0	0	0.42	7.63	8.78	8.78
Female	33	0.82	122.78	7.76	20.88	3.2	2.34	4.99	0.82	0.82	1.45	14.76	122.78	122.78
Race/ethnicity														
Non-Hispanic White	14	0.82	4.99	2.68	1.38	2.14	1.61	3.5	0.82	0.82	0.82	4.99	4.99	4.99
Black	20	1.47	14.76	4.41	3.31	3.21	2.46	5.08	1.47	1.47	1.54	13.15	14.76	14.76
Hispanic	29	0.63	122.78	7.52	22.3	2.61	1.96	3.85	0.63	0.63	1.54	11.8	122.78	122.78
Other	17	0	8.26	2.69	2.13	2.37	1.71	2.62	0	0	0	8.26	8.26	8.26
Dietary animal-protein-to-total-protein ratio (g)														
	N	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**0.50%**	**1%**	**5%**	**95%**	**99%**	**99.50%**
Overall	80	0	0.99	0.71	0.15	0.72	0.66	0.81	0	0	0.42	0.91	0.99	0.99
Age														
<55	34	0.58	0.92	0.74	0.09	0.73	0.66	0.83	0.58	0.58	0.61	0.9	0.92	0.92
55+	46	0	0.99	0.69	0.18	0.71	0.66	0.78	0	0	0.3	0.92	0.99	0.99
Gender														
Male	47	0	0.9	0.68	0.17	0.71	0.64	0.76	0	0	0.3	0.88	0.9	0.9
Female	33	0.45	0.99	0.76	0.11	0.76	0.7	0.83	0.45	0.45	0.59	0.94	0.99	0.99
Race/ethnicity														
Non-Hispanic White	14	0.45	0.83	0.69	0.11	0.68	0.62	0.78	0.45	0.45	0.45	0.83	0.83	0.83
Black	20	0.59	0.94	0.77	0.09	0.76	0.71	0.84	0.59	0.59	0.61	0.93	0.94	0.94
Hispanic	29	0.38	0.99	0.73	0.12	0.72	0.66	0.79	0.38	0.38	0.61	0.92	0.99	0.99
Other	17	0	0.89	0.63	0.24	0.7	0.63	0.72	0	0	0	0.89	0.89	0.89

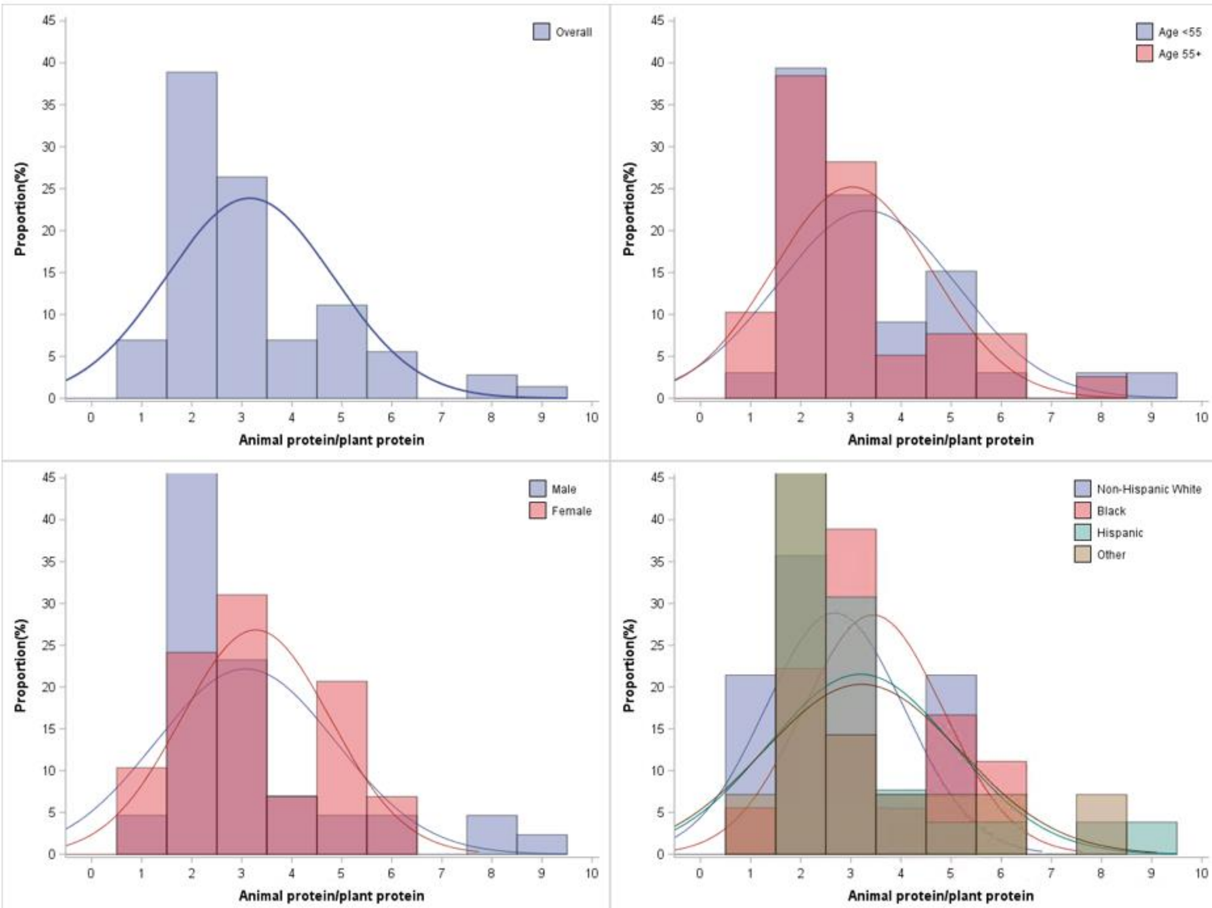
Dietary plant-protein-to-total-protein ratio (g)														
	N	**Min**	**Max**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**0.50%**	**1%**	**5%**	**95%**	**99%**	**99.50%**
Overall	80	0.01	1	0.29	0.15	0.28	0.19	0.34	0.01	0.01	0.09	0.58	1	1
Age														
<55	34	0.08	0.42	0.26	0.09	0.27	0.17	0.34	0.08	0.08	0.1	0.39	0.42	0.42
55+	46	0.01	1	0.31	0.18	0.29	0.22	0.34	0.01	0.01	0.08	0.7	1	1
Gender														
Male	47	0.1	1	0.32	0.17	0.29	0.24	0.36	0.1	0.1	0.12	0.7	1	1
Female	33	0.01	0.55	0.24	0.11	0.24	0.17	0.3	0.01	0.01	0.06	0.41	0.55	0.55
Race/ethnicity														
Non-Hispanic White	14	0.17	0.55	0.31	0.11	0.32	0.22	0.38	0.17	0.17	0.17	0.55	0.55	0.55
Black	20	0.06	0.41	0.23	0.09	0.24	0.16	0.29	0.06	0.06	0.07	0.39	0.41	0.41
Hispanic	29	0.01	0.62	0.27	0.12	0.28	0.21	0.34	0.01	0.01	0.08	0.39	0.62	0.62
Other	17	0.11	1	0.37	0.24	0.3	0.28	0.37	0.11	0.11	0.11	1	1	1

MADRAD, Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study.

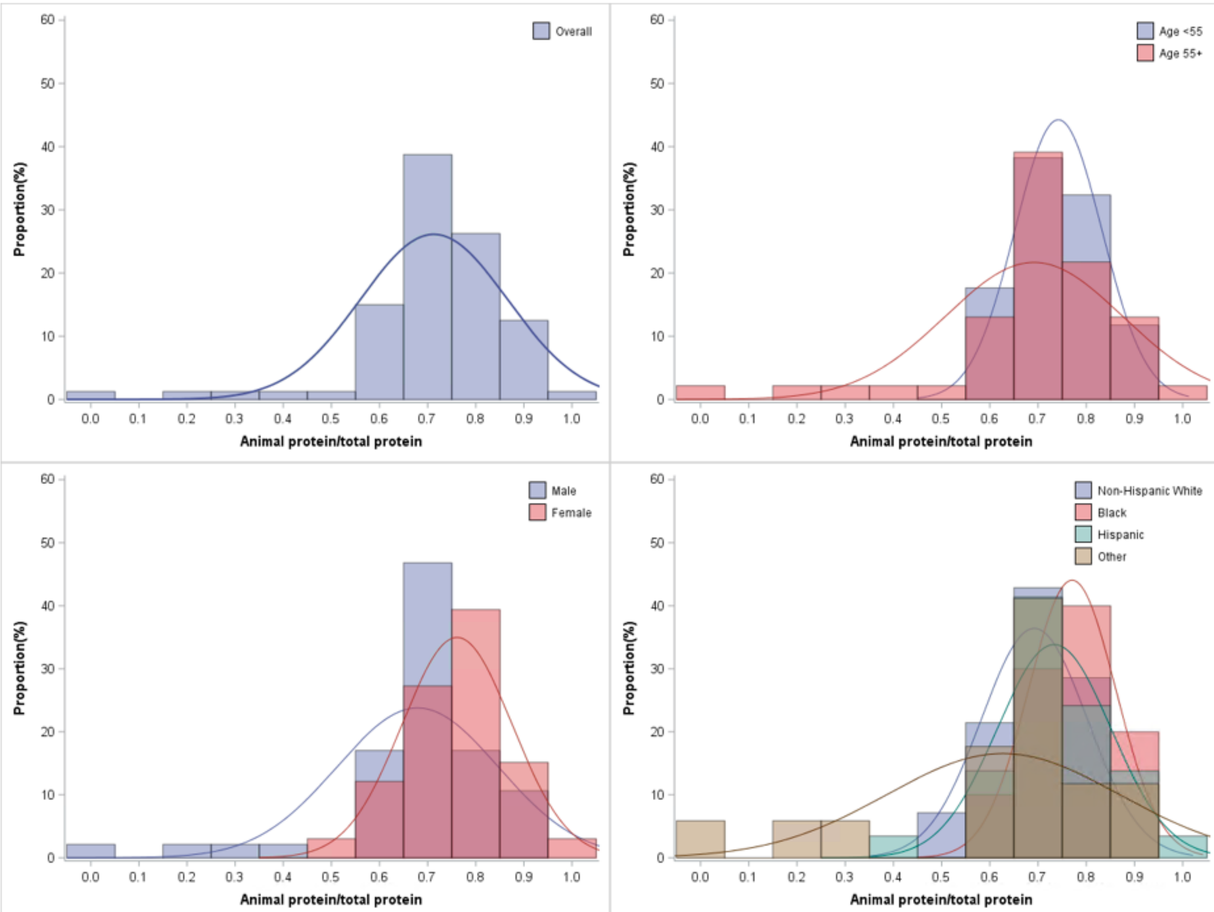
Supplemental Figure 2.1a. Among 80 hemodialysis patients in the MADRAD study with diet records, distribution of dietary phosphorus-to-animal-protein ratio (mg/g) in the overall cohort, <55 years old vs. ≥ 55 years old, male vs. female, and non-Hispanic White vs. Black vs. Hispanic vs. others, respectively.



Supplemental Figure 2.1b. Among 80 hemodialysis patients in the MADRAD study with diet records, distribution of dietary animal-protein-to-plant-protein ratio (g) in the overall cohort, <55 years old vs. ≥ 55 years old, male vs. female, and non-Hispanic White vs. Black vs. Hispanic vs. others, respectively.



Supplemental Figure 2.1c. Among 80 hemodialysis patients in the MADRAD study with diet records, distribution of dietary animal-protein-to-total-protein ratio (g) in the overall cohort, <55 years old vs. ≥ 55 years old, male vs. female, and non-Hispanic White vs. Black vs. Hispanic vs. others, respectively.



Chapter 4: Patient Perspectives on Diet and Adherence in Hemodialysis

Introduction

End-stage renal disease (ESRD) patients face a burdensome treatment regimen that typically includes thrice-weekly hemodialysis,[98] taking a myriad of medications,[41] and adhering to a restrictive list of dietary recommendations.[87] Among these recommendations include particular emphasis upon restriction of dietary intake of phosphorus, potassium, sodium, and fluid.[99] Potential consequences of failing to adhere to these critical dietary recommendations include adverse cardiovascular sequelae (i.e., congestive heart failure), as well as higher risk of hospitalization and death. For example, there is a large body of evidence demonstrating that, among dialysis patients, high serum phosphorus levels are associated with increased mortality risk.[1-3]

Previous literature suggests that non-adherence to dietary recommendations in ESRD patients may range anywhere from 22% to 81%.[28,29] However, it should be noted that existing studies that have analyzed dietary behaviors in hemodialysis patients have typically focused upon quantitative assessments of serum nutrient intake using laboratory tests, and/or structured surveys testing constructs of current health behavior theories. Given the recognition that nutritional status plays an important role in the health and survival of ESRD patients, there is a compelling need for greater study of the impact of patient health behaviors and attitudes upon dietary intake and outcomes in this population. Qualitative research studies are an important tool that may provide greater insight into these complex inter-relationships, such as patients' personal experiences of adhering to a renal diet in ESRD. Description of renal healthcare professionals' behaviors and understandings related to patient adherence are also meaningful outcomes of qualitative research. To our knowledge, there are no qualitative studies that have specifically investigated ESRD patients' perceptions of their diet and adherence in addition to describing actions and attitudes of their renal healthcare team members. Therefore, this reports aims to investigate hemodialysis patients' perceptions about their diet and factors related to adherence and describe characteristics of their renal clinicians.

Methods

Study Cohort

Two ESRD patients receiving thrice weekly hemodialysis treatments were interviewed from an outpatient dialysis unit in southern California. A convenient sampling approach was used to identify the patient cases.

Study Procedures

Two separate field observation visits were made to the dialysis center prior to conducting interviews with the patients. The first visit consisted of participating in weekly outpatient dialysis rounds during which the faculty nephrologist conducted individual rounds with patients. The second visit included weekly multi-disciplinary rounds that were conducted with the dialysis registered dietitian (RD). During these visits, patients received a nutritional "report card" from the RD that provided feedback about their nutritional status, serum levels of nutrients such as phosphorus and potassium. Following dialysis rounds, the RD was interviewed with in-depth questions regarding patients' diets and her perceived reasons for their diet-related behaviors.

On the third visit, semi-structured interviews with 12 open-ended questions were conducted with patients. Interviews were recorded, and notes were taken to document the patient's responses. The duration of each interview was approximately 25 minutes.

Following the patient interviews, recordings were transcribed. Notes from these interviews, observations from shadowing rounds, and the informal interview with the RD were all coded to uncover any recurring themes. A grounded theory approach was used to code the data in a two-step process. The preliminary coding involved identifying any and all various and unique ideas, issues and concepts within the data. The subsequent focused coding of these interesting topics was used to uncover common themes.

Results

The first patient was a 58-year-old Hispanic male who had been on dialysis for 5 years. The second patient was a 68-year-old Caucasian male who had survived over 2 years on dialysis. Both patients perceived themselves as "feeling good," and exercised great self-discipline in maintaining a healthy diet.

Developing adherence to the renal diet

Both patients described themselves as mostly following their dietary recommendations, however, they did not seem to have similar experiences in reaching this desired state of dietary adherence. Prior to starting dialysis, the first patient was obese, had type 2 diabetes, ate very poorly, and had previously suffered a stroke. He described the various stages he went through to go from dietary non-adherence to accepting the diet and complying with recommendations. A 'stages of change' theme emerged from these accounts. The stages began with a denial of the severity of his diseases.

> *"…you think these things aren't going to happen to you. Until they start. Once they start, it's like the kidneys and the blood pressure, especially being diabetic, that's why they always tell you, there's a magic number. 130 over. Never go above 130 because it damages the kidneys. And I thought, that's not gonna happen to me. But yup, sure enough. You see it slowly happening, and still, I think we always think, we're always in denial. It's not going to be too bad. And now well, now it happened."*

Overtime this patient experienced several negative consequences of his poor diet choices while on dialysis. He described how 'learning the hard way' was a part of his process in making better choices.

> "*If you don't keep your diet, you'll see, you'll know guys that are on dialysis that are real thin, and they're always [moves his hands in a motion as if to frantically scratch the skin all over his body], it's like they're playing an instrument, always scratching and itching. Because of the phosphorus, it builds up so much in your system, and they told me it gets under your skin and crystalizes. It's like you rolled in fiberglass. So you learn the hard way. Next time, I'll learn to keep away from that."*

The next stage in his process involved 'acknowledging benefits of the diet'.

> *"I know it's going to keep me alive another day. And yeah, I can trade that off and think that way and keep it positive. Or think this is a waste of time. But it's not. A waste of time was you not taking care of yourself, that's the main. So now, you learn."*

After being able to acknowledge the positive and negative consequences of certain diet choices, the patient seemed to undergo a change in mindset. Major motivators were a 'positive attitude', 'self-discipline', and goals related to feeling good and 'being comfortable'.

> "*And as far as the diet now, I look at it well, not keeping a diet the way I was supposed to got me into this situation. And now to live comfortably, because with dialysis, if you wanna live comfortable, I'll follow the diet no problem…the main thing is, you have to stay positive. Because nobody wants to join you in your pity party. And it doesn't do any good anyways to feel sorry for yourself."*

> *"…it can be very challenging…if you don't get yourself in that mindset."*

Finally, the patient combined several behaviors to 'create a system' that makes it easy for him to maintain a healthy diet. He has even figured out ways to 'cheat' on his diet without suffering any negative consequences. These behaviors helped him have a sense of 'control' over his diet.

> *"Well, Tuesdays, Thursdays, and Saturdays, I do not make any plans. My only plan is to make it to dialysis and get my dialysis. It's a lot easier than when you think that way…"*

> *"…there's a poster on the wall* (of the visitor waiting room)*…of the foods that you can eat and the foods that you can't eat. And why…I have that on my pantry, on my pantry door. So it's a constant reminder, when I go get something to eat, okay, I can't eat that. So it helps out. So that you catch yourself."*

> *"Another thing, to learn, if they give you binders, to take those with everything, so I don't mess up with that. I always keep my binders instead of a salt shaker, I keep those in front. So you never forget. Never forget. So when they put my plate, I automatically reach for the binders. The first thing I do is take my binders. Then I'll start eating."*

> *"It's very strict, but, you can cheat on it a little bit. You know, like beans. I'll have…just to get it outta my system, I'll have one little tiny spoonful, just to have the taste, and I'm over it. And yeah, and keep that."*

This patient also described having 'cultural food norms' that affected his dietary behaviors. He thought these norms sometimes made it difficult for him to fight off cravings.

> *"…the hardest part is…you tell a Mexican he can't eat beans or tortillas! Oh Lord, hehehe (laughing)! But ya know, hey. You put yourself in this situation, so lets look for a substitute. Let's look for a substitute. I think I can handle rice, white rice. Tortillas, I can eat flour tortillas, not corn tortillas. But, oh well."*

In contrast to the first patient, the second patient perceived himself as living a relatively healthy lifestyle prior to having kidney disease and was not certain as to why he developed the disease. He was of a normal body weight, exercised regularly and said that he was never a drug user or drinker. This patient thought that the dietary recommendations were relatively easy to follow. He did not seem to face any significant challenges or 'barriers' in being able to adhere to the recommendations.

> *"No real problems with it. It's something they establish and it's always on my mind, so it hasn't been that difficult."*

Maintaining adherence to renal diet

Even though these two patients started off with different perceptions of diet challenges and adherence, they currently had similar methods to keeping their diet and expressed similar ideas about what kept them focused. Among both patients, there was a theme of 'self-discipline' that kept them focused on shaping appropriate diet behaviors. Both patients accepted the status of their current condition and the responsibility of adhering to the diet. The patients and the RD recognized 'self-efficacy' as contributing to greater dietary success. Adequate 'diet knowledge' also seemed to be an important factor in patient adherence. Patients were keenly aware of specific nutrients to limit and foods to avoid.

Various aspects of 'social support' were also associated with diet adherence. The first patient identified his caregiver and wife as helping to keep him accountable with his diet. He emphasized the support he received from his wife, and recognized that doing things to make her happy made it easier for her to help him in return.

> *"Like I said I have my wife at home. And I take her my report card every month, so she looks to make sure that I am. And we put that on the refrigerator, okay, you're doing*

pretty good. So it makes me…well, it makes her happy. It makes me happy that I can make her happy. See, same thing…if you want to be happy, make her happy, ya know."

The first patient also found that his 'relationship with God' has especially helped him through challenging times.

> *"You learn how to pray. Because sometimes we don't have any other option, so you get a better relationship with God. And yeah, we don't thank him enough sometimes. I was one of those. Now, when I go for a walk, and I didn't realize that before. A simple thing like a walk. You can go for it, clear your head out. That's when you can work your relationship with God. You're out there walking by yourself. So you talk to God, hey Lord, ya know, I wish this wouldn't' be so hard, but, thank you for letting me enjoy the walk anyways. Yeah. The simple little things, and yeah, you talk to yourself and fill up your relationship with God and get your frustrations out."*

The second patient lived by himself, however, he perceived this to be an advantage in being able to stick to the diet. It was as if he did not have anyone to get in his way of doing what he was supposed to. Outside of the home, he thought that his sister was supportive with his diet. She is cognizant of the foods he cannot eat when she prepares food for him.

Connections with health behavior theories

There were several themes that emerged in being able to understand HD patients' perceptions of their diet and factors related to being adherent to their diet. Interestingly, several of these themes were related to various constructs of individual- and interpersonal-level theories of health behavior. For example the 'stages of change' theme correlates with the Transtheoretical Model of behavior (Figure 3.1). Constructs from the Health Belief Model such as 'perceived severity,' 'perceived benefits,' 'perceived barriers,' and 'self-efficacy' are similar to several themes that were uncovered in this study. In addition, the 'attitude' and 'perceived norms' constructs from the Theory of Planned Behavior could be applied to the current data.

And finally, the model of social support describes several constructs that are similar to the highlighted relationships between the patients and their family and medical staff we found in this study. Perhaps combining original themes found in this data with existing theoretical models could enhance our understanding of these patients' perceptions and behaviors.

Analysis of physician and RD behaviors and perceptions

Both patients perceived the physician and RD as being supportive and encouraging in setting dietary goals and being accountable. The patients seemed very comfortable talking to the physician and worked with him in a collaborative manner to tailor their treatment regimen. The physician spoke to the patients in simple language and displayed supportive body language such as standing by the patients' bedside and placing his hand on their shoulder. The patients thought that the RD asked appropriate questions and gave them easy-to-follow goals. The field observations suggested that both the physician and RD genuinely cared about their patients and stayed up-to-date with effective methods of communicating with patients.

The RD provided valuable insight into her perception about factors related to diet adherence in dialysis patients. For example 'mental health' played an important role, with signs of depression often associated with poor dietary adherence. The RD also identified 'previous food behaviors' as a contributing factor. For instance, many of the single male patient population she encountered usually depended on convenience foods most of which contain high levels of sodium and phosphorus. Many of these patients do not cook homemade meals, however, most of the nutrition education materials are based on whole foods as opposed to processed convenience foods.

Furthermore, the RD described 'making small changes' as an effective method of increasing positive dietary behaviors. She said that patients may feel overwhelmed by the many aspects of ESRD treatment, therefore it is helpful to give patients small goals at a time to build up their confidence. The RD also highlighted the importance of 'communication between the dialysis medical staff'. There emphasized the need for congruence between medical staff as to the patients' treatment plans so that these plans can be accurately communicated to the patient. She said that the patients will get confused with dietary recommendations if there is conflicting advice from their physician, nurse, RD, and other healthcare professional. A representation of factors influencing patient dietary behaviors from both the patient and RD perspective can be seen in Figure 3.2. Figure 3.3 is a depiction highlighting positive healthcare professional characteristics associated with patient dietary adherence.

Discussion:

The current qualitative investigation provided insights into hemodialysis patients' perspectives about their behaviors and attitudes related to following a renal diet. The study also examined characteristics and perspectives from the medical providers treating these patients.

Similar to the 'stages of change' theme we uncovered, Curtin et al. described how hemodialysis patients underwent a transformation to adopt behaviors that would potentially prolong life on dialysis.[100] Patients in their study described a restructuring of attitudes such that there was a reduced emphasis on an external locus of control and a subsequent adoption of responsibility for their survival. The authors suggested that factors such self-efficacy and self-preservation were related to the active self-management of ESRD.

A desirable goal discussed by our patients was having a sense of self-control over being able to adhere to the renal diet. Patients creating a sense of control involved following their diet, yet also knowing the boundaries for ‘cheating’ on their diet. They experimented to find out just how much ‘forbidden’ food and beverages they could tolerate without experiencing common side effects such as painful itching and fluid retention. Immediate side effects may influence behavior, but some patients are also motivated by wanting to increase their chances of receiving a kidney transplant[101] or by improving their survival and quality of life.[102]

In addition to the self-control needed to be adherent, there may be a hierarchy of control, where personal control is the first level, treatment and advice from medical professionals is the second level, and influence from a higher power is the third level.[102] Some patients believe that there are limitations to the influence of their own actions, therefore leading them to put faith in the advice of their medical team and/or a divine power.[102] The patients in our study respected the benefits of dialysis treatment and the recommendations given by their physician and registered dietitian. Some patients may develop this respect by suffering the negative consequences of being non-adherent, or, they may inherently trust and follow the prescribed treatment protocols. Patients in other studies thought that no matter what they did, or what the doctors did, everything was ultimately determined by God.[102] One of our patients voiced his trust in God’s plan, and expressed gratitude for the remaining good in his life.

Observations from our study revealed a positive collaborative relationship between the patients and clinicians, however, this type of relationship may not be universal. There have been reports of dialysis patients not feeling listened to by their healthcare providers[103], receiving limited justification for the use of phosphate binding medication[104], and not being provided with enough information about their test results and the progression of their illness[102]. In situations where there is a perceived imbalance of control, where the clinician is believed to have greater control compared to the patient, adherence levels tend to be lower.[105] Discrepancies between the patient's and clinician's perspectives about the etiology of the patient's ESRD works against a collaborative relationship and negatively affects patient outcomes.

Our study offered ideas for characteristics and actions of medical staff that promoted dietary adherence and a beneficial relationship with patients such as prescribing easy to follow goals, asking appropriate questions, and providing informative educational materials. There is a body of evidence which highlights the importance of a positive patient-physician relationship in improving patient outcomes.[106,107] Amidst the current increased attention to patient-centered approaches in healthcare, the physician-patient working alliance concept emphasizes the significance of the two-person, relationship-centered interactions in the treatment of chronic disease. To bolster the patient-physician alliance, Fuertes et al. recommends prioritizing improvement of factors such as identification of patient obstacles, goal setting, agreement communication, and fostering trust through active listening, empathy, and non-verbal communication.[106]

Some patients admit to being confused or frustrated with the renal dietary recommendations, particularly if it contradicts what they believe constitutes a 'healthy' diet or dietary advice for comorbid conditions such as cardiovascular disease and diabetes.[101] Patients in other studies have reported they prefer that individualized dietary recommendations be given at diagnosis by a registered dietitian, and should be written in a simple format.[103] Some patients would appreciate it if the RD were completely open and honest about the consequences of being non-adherent to the renal diet. Patients have suggested that dietary counseling should be continuous since conditions vary throughout the course of the disease. The RD in our study expressed the need for conformity of nutrition advice among the multidisciplinary healthcare team, and this was also a sentiment recommended by patients in another study.[103] These patients suggested that the RD should educate the healthcare staff on the components of a renal diet.

In order for a RD to make an individualized recommendation about what a patient should eat, they should conduct an assessment of the patient's current dietary habits. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend for RD's to collect patient dietary intake data biannually with a dietary interview or diary.[108] Unfortunately, many renal dietitians may lack the time and resources to thoroughly make these assessments. In a study by Hand et al., only 6.5% of renal RD's reported assessing patients' dietary intake biannually, while 70% conducted the assessment only when laboratory tests were abnormal.[59] RD's reported lack of software and time as reasons for not conducting dietary assessments more frequently.
While 8% of RD's assessed diets with a 3-day diet record, 50% used a typical day recall method. Sixty-two percent of RD's analyzed nutrient intakes by estimation "in their head," whereas 24.5% calculated intakes by hand.

Our observations suggested the important nature of social support from several sources, such as family and the healthcare staff. Social support from friends and family can play a role in hemodialysis patients' adherence to dietary, fluid, and medical care recommendations[35,109], where greater support is associated with greater adherence. Hemodialysis patients have also expressed a desire for and an appreciation of peer support, whether it be in a group or a one-on-one setting.[103,110,111] Established hemodialysis patients can provide valuable information about their experiences, and are able to contribute a unique sense of understanding, empathy, and hope for the future.[111] These patients can also become role models by encouraging empowerment over dietary recommendations and by normalizing adherence.

Our study was limited by the small number of cases and by collecting data at only one hemodialysis clinic. However, our study was unique in being able to gather a robust amount of data due to the combined observations from patients and their clinicians.

This study investigated hemodialysis patients' perceptions of the renal diet, behaviors and attitudes of renal clinicians, and how they related to adherence. A future study would include more cases where the total number of cases selected would be determined by when the data reached a level of saturation.

Figure 3.1. Stages of change in renal diet attitudes and behaviors among hemodialysis patients

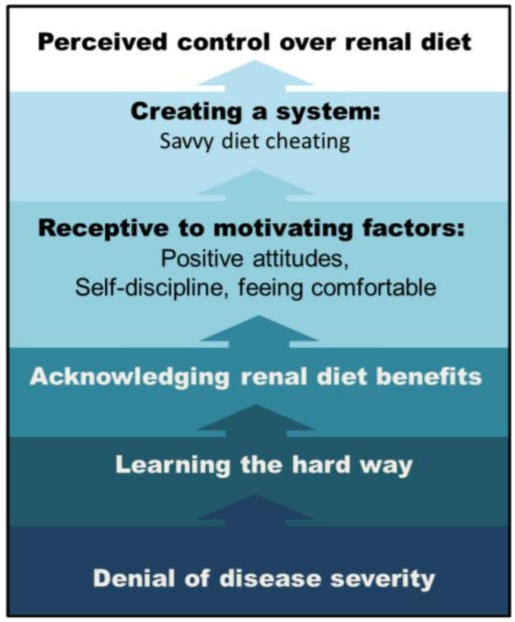


Figure 3.2 Representation of hemodialysis patient and RD perspectives on factors influencing individual dietary behaviors

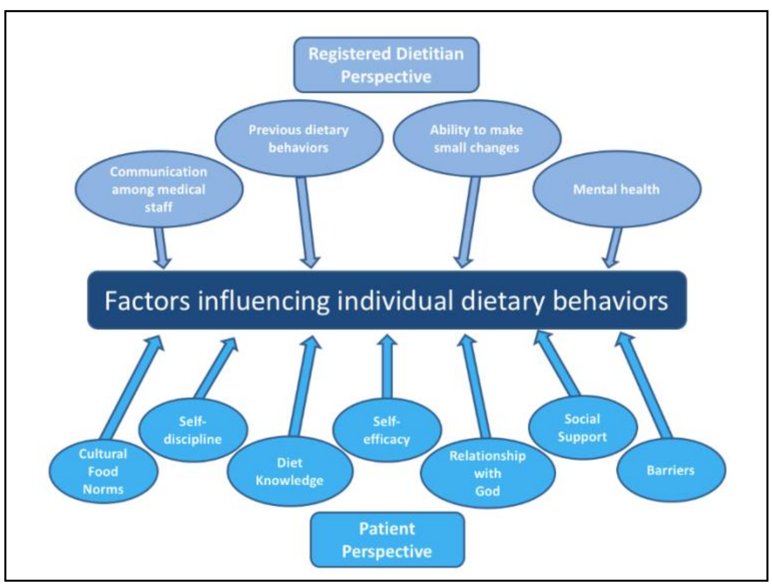
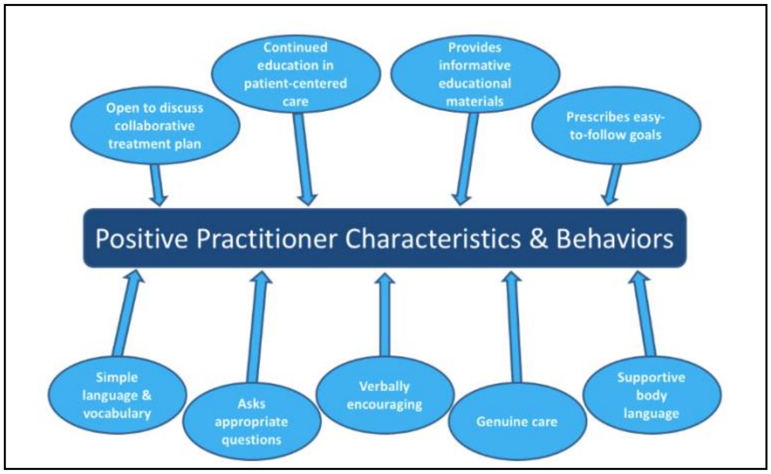


Figure 3.3. Representation of positive clinician characteristics and behaviors associated with hemodialysis patient dietary adherence



Conclusion

Summary of Main Findings

In Chapter 2, it was discussed that current dietary recommendations for dialysis patients suggest that high phosphorus diets may be associated with negative outcomes such as increased serum phosphorus and death. However, caution must be practiced to ensure dietary phosphorus intake is not compromised at the expense of dietary protein intake. It was hypothesized that higher concentrations of dietary phosphorus intake would be associated with higher mortality among a diverse cohort of hemodialysis (HD) patients. Among 415 patients from the prospective multi-center Malnutrition, Diet, and Racial Disparities in Kidney Disease Study, the association of absolute dietary phosphorus intake, ascertained by food frequency questionnaires, with all-cause mortality using multivariable Cox models was examined. In secondary analyses, the relationship between dietary phosphorus scaled to 1000 kcal (mg/kcal) and dietary phosphorus-to-protein ratio (mg/g) with survival was also examined.

In analyses adjusted for expanded case-mix+laboratory+nutrition covariates, the lowest tertile of dietary phosphorus intake was associated with higher mortality risk (ref: highest tertile): adjusted HR (aHR) (95%CI) 3.33 (1.75-6.33). In analyses of dietary phosphorus scaled to 1000 kcal intake, the lowest tertile of intake was associated with higher mortality risk compared to the lowest tertile: aHR (95%CI) 1.74 (1.08, 2.80). Similarly, in analyses examining the association between dietary phosphorus-to-protein ratio, the lowest tertile of intake was associated with higher mortality risk compared to the lowest tertile: aHR (95%CI) 1.67 (1.02-2.74). Results of this study suggest that lower intakes of dietary phosphorus were associated with higher mortality risk. Further studies are needed to clarify the relationship between sources of dietary phosphorus intake and mortality in HD patients.

In Chapter 3, my goal was to gain insight into dietary phosphorus intakes and related dialysis patient clinical and sociodemographic characteristics. Three-day diet records from 80 dialysis patients enrolled in the MADRAD study were collected. In primary analyses, we conducted logistic regression analyses examining the association of sociodemographic, comorbidity, dialysis treatment, health insurance, and dietary intake characteristics with likelihood of above median dietary intakes of phosphorus-to-total-protein ratio, phosphorus-to-plant-protein ratio, phosphorus/1000 kcal, and plant-protein-to-total-protein ratio, respectively. Distribution of nutrients overall and according to subgroups was summarized.

It was found that predictors of high phosphorus-to-plant-protein ratio included Black race and female sex, while older age was a predictor of low intake. Female sex was a predictor of high phosphorus/1000 kcal. Predictors of low plant-to-total-protein ratio were female sex, Black race, and being single. Older patients had lower phosphorus-total-protein ratio, lower phosphorus-to-plant-protein ratio, lower phosphorus/1000 kcal, and higher plant-protein-to-total-protein ratio. Compared to males, females had similar phosphorus-to-total-protein ratio, higher phosphorus-to-plant-protein ratio, higher phosphorus/1000 kcal, and lower plant-protein-to-total-protein ratio. Non-Hispanic Whites had the greatest dietary intakes of plant-protein-to-total-protein ratio, Blacks had the highest dietary intakes of phosphorus-to-plant-protein ratio, and Hispanics had the greatest dietary intakes of phosphorus/1000 kcal and phosphorus-total-protein ratio. I concluded that predictors of dietary phosphorus and plant-protein intake included Black race, female sex, older age, and being single. Individual differences in patient dietary intake should be respected and individualized dietary recommendations are necessary. Future studies analyzing the association between these nutritional measures with clinical outcomes such as mortality are warranted.

In Chapter 4, I used a qualitative approach to offer nuanced insights into the complex nature of dietary behaviors and related factors such as the patient's personal experience and influential characteristics of renal clinicians. This case study investigated patients' perceptions about their diet and clinician-related factors related to dietary adherence. A semi-structured interview was conducted with two male hemodialysis patients. Their renal staff physician and registered dietitian were also observed. Notes from the interviews and observations were coded to uncover any recurring themes. A grounded theory approach was used to code the data.

Factors associated with patient dietary adherence included social support, self-efficacy, self-discipline, barriers, and cultural food norms. A 'stages of change' theme emerged from these accounts where the patient went from denying the severity of his disease, nearly giving up on treatment, to gaining perceived control over his diet and disease. Both patients perceived the physician and RD as being supportive and encouraging in setting dietary goals and being accountable. The field observations revealed that both the physician and RD genuinely cared about their patients and stayed up-to-date with effective methods of communicating with patients. The high mortality rate of patients within the first few years of dialysis initiation amplifies the critical need to uncover methods of helping patients to overcome potential barriers. The results of this study highlights the importance of understanding the complexities of HD patients' perceptions about their diet and adherence, and could possibly be used to create treatment interventions that would improve health outcomes in these patients. Further qualitative studies should be conducted to include more participants and interviews with medical staff to create a more robust analysis of diet and adherence in this ESRD population.

Limitations

Several limitations bear mention within the studies of this dissertation. First, a limitation of dietary assessment methods, including FFQs and 3-day diet records, is that they tend to underestimate actual dietary intake.[55] In our qualitative analyses, this was compensated for by using relative values in addition to absolute values of nutrient intakes. A limitation of the FFQ is that it is unable to list every type of food typically eaten by hemodialysis patients and therefore some phosphorus containing foods may be underrepresented in the questionnaire. The software used to analyze the contents of the 3-diet records is also limited in that while it has an extensive breadth of foods, it is not an exhaustive list, and therefore may underestimate the nutrient content of some foods. Researchers, RDs, and consumers alike are limited in their knowledge of the exact amount of total phosphorus and type of phosphorus (organic versus inorganic) contained within foods.[74] Unfortunately, the food industry is only required to list phosphorus additives in ingredients lists, but is not required to state the amount or kind of phosphorus within a food.[112]

In our studies in Chapters 2 and 3, we were limited by using dietary data collected at a single point in time and were not able to account for any seasonal variations in dietary behaviors. For example, the seasonal availability of certain types of produce may create dietary intake differences within and between patients. In Chapter 3, we were unable to obtain patient serum phosphorus data and our study was not long enough to collect mortality data. Because of this, we could not describe how phosphorus intake as assessed by 3-day diet records translates into serum phosphorus concentrations and risk of mortality.

Moreover, all of our studies were conducted with a racially and ethnically diverse cohort within southern California. Therefore our results may not be generalizable to the greater dialysis patient population. Furthermore, a selection bias may have occurred if the patients who declined to participate in our study had different dietary habits than those who did participate. Even though a robust amount of information was collected in our qualitative study in Chapter 4, our two patients and their clinicians may have been unique in their attitudes and characteristics.

Lastly, due to the nature of observational studies, we were not able to confirm a causal association between dietary phosphorus intake and mortality in Chapter 2.

Progress in Clinical Practice and Future Research

The KDOQI guidelines have created the leading set of recommendations for clinical performance measures in HD patients, informing ESRD policies created by Medicare and Medicaid Services in the United States.[113] Objectives of these guidelines include improving efficiency of care, increased patient quality of life, decreased patient morbidity, and improved patient survival. The KDOQI is based on compelling evidence from multidisciplinary medical literature. Even though the current literature has established that hyperphosphatemia is associated with an increased risk of mortality, there is limited and conflicting evidence about the relationship between dietary intake of phosphorus and mortality.

The results of our analysis in Chapter 2, where lower intakes of dietary phosphorus was associated with greater risk of mortality, contradicts the current KDOQI recommendation for dialysis patients to implement a low phosphorus diet. In an effort to reduce dietary phosphorus and other critical nutrients such as potassium, dialysis patients may reduce intake of whole foods such as legumes, whole grains, vegetables, and fruits. A diminished intake of these foods will also reduce consumption of antioxidants, phytonutrients, and fiber. This is potentially at the detriment of heart health, of particular importance since most dialysis patients die from cardiovascular disease.[85]

In order to counteract reductions of heart-healthy nutrients in dialysis patients, there has been an emergence of research and clinical practice with an emphasis on liberalizing the renal diet.[114] This practice involves encouraging intake of whole nutritious foods, with a concurrent prioritization of educating patients on reducing their intake of processed food additives. It must be recognized that food is not simply a factor tied to risk of morbidity and mortality, but it is also a source of comfort, is connected to emotions, and influences quality of life.

In a study by Welte et al. on renal RD diet liberalization practices, it was reported that most RDs felt confident in finding, interpreting, and applying evidence based literature to their practice.[115] A majority of the RDs reported sometimes recommending avoidance of legumes and whole grains, and recommended avoiding inorganic phosphorus additives. Only a minority of the surveyed RDs felt that it was acceptable to liberalize restrictions on vegetables, whole fruits, whole grains, and legumes.

In order to improve the precision of dietary phosphorus recommendations and clarify the efficacy of liberalized diets, there should be an evolution in the research surrounding dietary phosphorus intake among dialysis patients. Since inorganic phosphorus additives lack nutritional benefits and have nearly 100% absorbability, future research could focus on long-term randomized controlled trials investigating associations between risk of mortality and diets containing whole foods and low-to-no phosphorus additives. There could also be qualitative analyses comparing perspectives and quality of life of patients following the traditional restrictive renal diet versus those following a more liberal diet with focused elimination of phosphorus additives.

Even if there was an association found between a whole foods, low phosphorus additive diet and increased survival among dialysis patients, there would still need to be a change in how the food industry labels foods. Since it is not required to list the total and added phosphorus quantity on nutrition labels, assessments of dietary phosphorus will continue to be underestimated. The Academy of Nutrition and Dietetics recommended that the U.S. Food and

Drug Administration require the addition of total and added phosphorus quantity on the revised nutrition facts labels, however, this was not implemented.[116] An encouraging step lies in the proposal of the Food Labeling Modernization Act of 2018, in which labeling of phosphorus quantity was requested as an addition to nutrition facts labels.[117] This Act currently resides in the U.S. House of Representatives.

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