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Plant-based diet to delay the progression of chronic kidney disease

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BOSTON UNIVERSITY
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Thesis

**PLANT-BASED DIET TO DELAY THE PROGRESSION OF CHRONIC
KIDNEY DISEASE**

by

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PLANT-BASED DIET TO DELAY THE PROGRESSION OF CHRONIC

KIDNEY DISEASE

JUSTIN KOEHL

ABSTRACT

Background

Chronic kidney disease is an insidious, long-term disease, characterized by progressive decline in kidney function over time. It currently affects millions of Americans, and millions more are at risk to develop the disease in the future. There is no cure-all treatment for chronic kidney disease. Current management involves slowing the progression in the decline of kidney function, managing associated comorbidities that contribute to the disease, including hypertension and type 2 diabetes mellitus, and treating disease complications. The overall goal of treatment is to delay the time to dialysis and reduce the risk of cardiovascular events. Current management also involves a set of dietary restrictions.

Literature review

Studies that have been conducted using the current dietary recommendations have been shown to have some benefit. However, other studies have demonstrated no advantage using these dietary guidelines. Few studies have looked at how the source of food affects renal function over time. A review of the literature will highlight the importance of the source of food consumption for patients with chronic kidney disease.

Proposed project

The study being proposed is a randomized-controlled trial comparing current dietary recommendations with a plant-based diet for patients with chronic kidney disease. The study participants will have a baseline assessment of renal function with follow-up throughout. The trial will last for 36 months. The primary outcome being measured is the change in estimated glomerular filtration rate over time with secondary outcomes being urinary albumin levels, serum bicarbonate, and serum phosphorus.

Conclusion

The data from this trial will help conclude if a plant-based diet is more effective than a traditionally recommended diet at delaying the decline in glomerular filtration rate for patients with chronic kidney disease.

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LIST OF ABBREVIATIONS

ACR.....	Albumin Creatinine Ratio
AER.....	Albumin Excretion Rate
BMC.....	Boston Medical Center
CKD	Chronic Kidney Disease
CKD-EPI.....	Chronic Kidney Disease Epidemiology Collaboration Equation
GFR.....	Glomerular Filtration Rate
KDIGO.....	Kidney Disease Improving Global Outcomes
KDOQI.....	Kidney Disease Outcomes Quality Initiative
MDRD.....	Modification of Diet in Renal Disease
NFK.....	National Kidney Foundation
NHANES.....	National Health and Nutrition Examination Survey
USRDS.....	United States Renal Data System

INTRODUCTION

Background

Chronic kidney disease, or CKD, is a disease characterized by a gradual loss in kidney function over time. This includes a spectrum of different disease mechanisms that damage the kidneys, resulting in a decreased ability for the kidneys to perform their normal physiological functions. Millions of Americans currently have chronic kidney disease, while millions more are at an increased risk to develop this condition in time. Chronic kidney disease can have a wide range of presentations and courses. There are patients who have stable disease, characterized by a slow progression in loss of kidney function with few complications of the disease, while other patients may decline at a much faster rate and experience several complications. As the disease course reaches its end it becomes known as end-stage renal disease, in which renal replacement therapy or dialysis are the end line treatments.

Because so many Americans are affected by this disease, early detection is key. This will allow the disease to be managed timely, in hopes of slowing the decline in kidney function. Current treatment and management is very complex. Controlling comorbidities associated with CKD, such as hypertension and diabetes, is critical for management. As the disease progresses, treating complications are crucial for both quality of life and survival for these patients. Treatment involves both medications and lifestyle modifications, including diet and physical activity. With early detection and

regular follow-up, CKD can be managed properly, thus preserving kidney function for a longer period of time.

Due to the insidious and progressive nature of CKD, lifestyle modifications is particularly important for management, specifically diet. Diet has been demonstrated to be a target for potentially slowing the decline in kidney function, reducing kidney injury, and managing disease complications, all while having a positive impact on associated comorbidities. Current dietary recommendations are moderate protein intake, salt restriction, and specific electrolyte target goals guided by lab values. The overall goal of dietary management is provide enough nutritional value to maintain a healthy weight and muscles mass and provide enough energy for daily living, while avoiding the buildup of metabolic wastes and further cause of injury.

Statement of the Problem

Because millions of Americans are affected by CKD and millions more are at risk, the burden of CKD on public healthcare costs is very high. There is no cure-all for CKD, which means once a patient is diagnosed they need to be treated and managed for a lifetime. This makes dietary modification vital for management. While some diets have shown promise in slowing chronic kidney disease decline, no diet has been established as the optimal diet. Clinical trials have shown conflicting evidence when comparing certain dietary patterns, making it not entirely certain what the most advantageous diet is.

With proper and optimal dietary management patients would have improved quality of life, less disease complications, and potentially a slower progression in the decline of renal function. This would not only prolong life, but could also null the amount of medications people need to take, while delaying the need for renal replacement therapy or dialysis. Furthermore, better dietary management may also treat associated comorbidities and risk factors of CKD, which may further help protect the kidneys from more decline in function.

Hypothesis

A whole-food, plant-based diet consisting of fruits, vegetables, whole grains, and legumes will preserve or slow the progression of chronic kidney disease compared to a traditionally recommended diet.

Objectives and specific aims

The implementation of a plant-based diet will slow the progression of chronic kidney disease while improving disease complications. This would give patients a better quality of life, decrease mortality, and delay the need for end-stage treatment options such as renal transplant surgery or dialysis. A plant-based diet will also provide this patient population with sufficient nutritional value that will allow them to maintain a healthy weight and have enough energy to carry out daily living.

1. Compare a plant-based diet with other diets to assess its overall affect on delaying or preserving the progression of chronic kidney disease
2. Demonstrate the ability of a plant-based diet to treat other disease complications compared to current dietary or therapeutic recommendations.

REVIEW OF THE LITERATURE

Overview

What is chronic kidney disease?

Chronic kidney disease includes a spectrum of different pathophysiological mechanisms that leads to impaired kidney function and a progressive decline in the glomerular filtration rate. CKD is defined as the presence of kidney damage or decreased kidney function for more than 3 months, regardless of the underlying cause. Kidney damage can be detected as a urinary albumin excretion $\geq 30\text{mg/day}$, while decreased kidney function is assessed by an estimated glomerular filtration rate of $<60 \text{ mL/min/1.73m}^2$. The role of eGFR and urine albumin will be discussed below. The NKF-KDOQI and KDIGO have both developed a classification system based on eGFR and albuminuria that stratifies patients to guide management and predict risk of progression and complications.

Table 1. CKD Classification based on eGFR. ¹

GFR Stages	GFR (mL/min/1.73m ²)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5(D)	<15	Kidney failure (add D if treated by dialysis)

Table 2. CKD Classification based on Albuminuria.²

Albuminuria Stages	AER (mg/day)	ACR (mg/g)	Terms
A1	<30	<30	Normal to mildly increased
A2	30-300	30-300	Moderately increased
A3	>300	>300	Severely increased

As the above classification systems suggest, chronic kidney disease is a lasting, progressive disease. The pace at which the disease progresses varies from individual to individual. Some patients may live their entire lives asymptomatic with a stable GFR, while others may decline more rapidly and have several disease complications. As the disease course reaches its final stage, it becomes known as end-stage renal disease. It is at this stage when considerations are made for dialysis or renal replacement transplant therapy. While there is no cure for CKD, proper lifestyle modifications, management, and treatment can aid in a slower progression, and in some cases even prevent it.

Epidemiology of chronic kidney disease

According to the National Kidney Foundation, it is estimated that 26 million Americans have CKD, with millions more being at an increased risk to develop the disease.³ The 2016 USRDS Annual Data Report shows that the prevalence of CKD among participants in the Health and Nutrition Examination Survey is currently at 14.8%.⁴ Among the patient population with a known diagnosis of CKD, stage 3 represents the most prevalent

stage of disease course in regards to GFR, while an ACR of <10 mg/g is the most prevalent distribution of albuminuria.⁴ CKD occurs most in individuals > 60 years of age (32.6%), and affects females (16.5%) more than males (13.0%).⁴ However, males comprise 57.3% of all patients receiving treatment for chronic kidney disease compared to women at 42.7%. More males are also on dialysis or living with a functioning kidney transplant when compared to women.⁵ Among race, African-Americans have the highest prevalence of CKD (16.9%), while Non-Hispanic Whites have the second highest at (15.2%).⁴

Chronic kidney disease has several known risk factors which are clinically relevant for both screening and early detection of the disease. Risk factors include increasing age, presence of diabetes mellitus, hypertension, cardiovascular disease, metabolic syndrome, increased body mass index, family history of end-stage renal disease or chronic kidney disease, and a history of acute kidney injury. It is estimated that 40% of individuals with CKD have diabetes, 32% have hypertension, and 40% have self-reported cardiovascular disease.⁴ The role of these comorbidities will be discussed in more detail below.

Pathophysiology of chronic kidney disease

Chronic kidney disease can be the result of several different pathophysiological mechanisms. While each disease process may be different, the end result is always abnormal kidney function or a decline in the filtering ability of the kidney. The two

leading causes of CKD are diabetes mellitus and hypertension. CKD that results from diabetes is known as diabetic glomerular disease or diabetic nephropathy. CKD resulting from hypertension is known as hypertensive nephropathy, and can be either a primary glomerulopathy with hypertension or vascular and ischemic renal disease. Other less common causes of CKD include a group of diseases collectively known as glomerulonephritis, autosomal dominant polycystic kidney disease, and other cystic and tubulointerstitial nephropathies. While the underlying cause of CKD may be different, there are two basic maladaptive mechanisms that occur resulting in kidney damage.

The first mechanism that occurs is specific to the underlying etiology of the cause of CKD. This could be due to inflammation, immune complex deposition, uncontrolled blood glucose levels, hypertension, or even genetically smaller kidneys. Regardless of the etiology, this results in nephron loss. The second mechanism that occurs is irrespective to the underlying cause of nephron loss and kidney damage. Initially these changes are adaptive, as the remaining nephrons undergo a process of hyperfiltration and hypertrophy which helps preserve glomerular filtration rate. However, over time these changes have an overall negative effect on kidney function. The increased pressures and flow to the kidney result in structural changes, resulting in further nephron loss and sclerosis of kidney tissue. The renin-angiotensin system plays a major role in the development and progression of these changes.⁶ This process can take years, which explains the slow progression and insidious nature of the disease course.

Because diabetes mellitus and hypertension are the two leading causes of chronic kidney disease, and due to the fact that these underlying conditions often occur together, the shared pathophysiology will be looked at a bit more closely. Uncontrolled systemic hypertension and elevated blood glucose levels can lead to increased glomerular wall stress, direct endothelial cell damage, and renal vasodilation. These insults result in structural and hemodynamic changes to the kidneys which cause the compensatory mechanisms above to occur. These changes, along with long-term intraglomerular hypertension and increased strain on the microvasculature cause cytokine release, such as transforming growth factor-beta, which result in further kidney injury. The end result of this pathogenesis is a histological manifestation known as focal segmental glomerulosclerosis, ultimately ensuing clinical signs and symptoms of disease.

Complications of chronic kidney disease

The kidneys perform several important functions for the human body. Other than filtering blood and removing wastes, the kidneys also play a role in fluid and electrolyte balance, acid-base homeostasis, blood pressure regulation, and producing hormones vital for red blood cell production and bone and mineral metabolism. Because the kidneys play such a vital role in so many body processes, several complications can arise when an individual has chronic kidney disease. These complications occur at different stages of the disease course. Below is a table summarizing some of the major complications of CKD. Some of

these complications will be discussed in further detail below because the management of these problems can have a direct effect on disease progression.

Table 3. Complications of CKD.

System	Complication
Water Balance	Volume overload
Electrolytes	Hyperkalemia
Acid-Base	Metabolic acidosis
Bone and Mineral	Hyperphosphatemia, secondary parathyroidism, vitamin D deficiency
Hematological	Anemia
Cardiovascular	Hypertension, cardiovascular disease
Lipid Metabolism	Dyslipidemia

One complication that deserves further attention is the acid-base disturbance that occurs in CKD; metabolic acidosis. During the early stages of the disease the kidneys are able excrete enough titratable acid with the remaining nephrons present, however, as the GFR declines to stage 3 and lower, the kidneys are no longer able to remove a sufficient amount of acid from the body. Patients who have CKD with a metabolic acidosis have been shown to have an association with increased mortality and faster disease progression.^{7,8} Current dietary guidelines recommend treating metabolic acidosis in CKD patients when the serum bicarbonate falls to <22 mEq/L with Na⁺-based alkali therapy.⁹

This has been shown to be renal protective and slow the disease course, making the treatment of this complication imperative for disease management.

A second important complication that occurs in CKD is hyperphosphatemia. The retention of phosphorus begins early in chronic kidney disease, while evident hyperphosphatemia becomes more severe in stages 3-4 of the disease course. Hyperphosphatemia is one of the initial triggers that leads to the bone and mineral disorders that occur in CKD. This occurs because of two underlying mechanisms. In the early stages of CKD the remaining nephrons available are able to maintain phosphate excretion through increased tubule reabsorption, mediated by fibroblast growth factor 23 (FGF23). However, through a variety of complex feedback loops involving several other hormones and electrolytes between the kidneys, intestines, bones, and vascular system, phosphate levels slightly rise. As GFR continues to decline more phosphate is retained, which further contributes to the other hormonal and electrolyte imbalances seen in bone and mineral disorder. Current guidelines recommend dietary phosphate restriction to .08-1.0 g/kg/day, followed by the use of phosphate binders when diet restriction is no longer adequate. Treatment is guided by close monitoring of serum values. Hyperphosphatemia has been shown to increase mortality in chronic kidney disease¹⁰, which makes the treatment of this complication vital for CKD management.

Measuring disease progression and severity

Once an individual is diagnosed with chronic kidney disease, the next most important step is to determine the degree of abnormal kidney function and how rapidly the disease is progressing. Nephrologists use several parameters including estimated glomerular filtration rate, urinary markers and sediment, and serum markers to evaluate the kidneys. All of this data will be evidence for how much kidney dysfunction is present, how far the disease course has progressed, and manifestations of any complications. As mentioned before, two important parameters are eGFR and urine albumin.

The glomerular filtration rate is the sum of the filtrating ability of all viable nephrons. Therefore, an eGFR gives a rough measure of how well the kidneys are filtering the plasma and the number of properly function nephrons. GFR can be variable from person to person, as it is affected by age, weight, race, serum markers, and body composition. Because so many factors can affect an eGFR, estimation equations have been developed that utilize demographic and clinical variables to make a more accurate estimation of GFR. While several estimation equations exist, the two most common are the MDRD and CKD-EPI equations. The limitations and advantages of both of these estimation equations will be discussed in more detail in the methods section.

The other method for assessing kidney function and injury is by measuring serum markers and urinary sediment. These act as clinical predictors for both the extent of nephron injury and acceleration of progression. Blood pressure should always be trended, as normal blood pressures have been associated with the preservation of GFR.¹¹ The amount of proteinuria present should also be monitored. Higher levels of urinary protein

excretion have been associated with a more rapid decline in GFR¹², while a reduction in proteinuria has been shown to slow the progression of renal disease.¹³ A metabolic panel will indicate the presence of any electrolyte imbalances, including abnormalities with sodium, potassium, phosphate, and calcium, while also unveiling the presence of any acid-base disturbances with serum bicarbonate. This panel will also show serum levels of BUN and creatinine which are indirect markers of kidney function, as these variables are included in GFR estimation equations. Lipid levels, including LDL-cholesterol and HDL-cholesterol will be routinely checked as well. Finally, a complete blood count will unveil the presence of anemia.

Prognosis of chronic kidney disease

The prognosis of chronic kidney disease is influenced by several different factors, which makes the disease course highly variable among individuals. The rapidity of disease progression is influenced by the underlying cause of kidney injury, presence of comorbidities, socioeconomic status, genetics, response to treatment, and ethnic background. Some patients will remain asymptomatic with a stable GFR for their entire life, while others will have a more rapid decline and several disease sequelae with eventual progression to end-stage renal disease.

According to the USRDS, the current mortality rate for individuals with CKD after being adjusted for age, race, and sex is 113 deaths per 1,000 patient years at risk.⁴ Currently, the transition from an eGFR of $>60 \text{ mL/min/1.73m}^2$ to $<60 \text{ mL/min/1.73 m}^2$ is

0.5 percent per year, while the transition from an eGFR of 15-60 mL/min/1.73m² to end-stage renal disease is 1.5 percent per year. The Multiple Risk Factor Intervention Study showed that a combination of low eGFR and proteinuria was associated with a significant increased risk of disease progression versus either variable alone.¹⁴ Current life expectancy of patients over 50 with a normal eGFR and ACR is 35.2 years. An eGFR of <60 mL/min/1.73m² is associated with a reduction in life expectancy of 5 years, while an ACR of >30 mg/g is associated with a reduction of 5.8 years. When both variables are present together, life expectancy drops by 11.8 years.⁴

CKD is also an independent risk factor for cardiovascular disease. Cardiovascular disease among individuals with chronic kidney disease results in death more than actual progression to end-stage renal disease.¹⁵ In patients aged 66 and older, the prevalence of cardiovascular disease is 66.8%, while only 43.1% in patients who do not have CKD. Chronic kidney disease and cardiovascular share a close and complex relationship in part due to the shared similarities in pathophysiology, as well as the overlap of several important risk factors. A decline in eGFR and increase in ACR increase the risk for cardiovascular disease. Patients with CKD have a higher risk of death from cardiovascular disease versus the need for renal replacement therapy. This makes the prevention and management of cardiovascular disease critical for patients with CKD.

Chronic kidney disease and healthcare costs

According to the Center for Disease Control, chronic kidney disease is the ninth leading cause of death in the United States. From 2013 to 2014, there was a decrease in hospitalizations among patient with CKD by 7.4%.⁴ Hospital readmission rates were also slightly decreased from 2013 to 2014, with a readmission rate of 21.4% for CKD patients. Although the trend of hospitalizations and readmissions is decreasing, the burden of chronic kidney disease is still seen in healthcare costs. Both CKD and ESRD are very expensive to treat, and these two conditions alone represent 25% of the Medicare budget.¹⁶ According to the most recent numbers from the National Kidney Disease Education Program, CKD costs \$57.5 billion in health care costs in the United States.¹⁷ This makes efficient and proper management crucial not only for the individual affected by chronic kidney disease, but for the healthcare system overall.

Chronic kidney disease and diet

While no single diet has been proven with clinical certainty to be the sole best for chronic kidney disease, there are several guidelines that have showed some promise in affecting clinical outcomes in patients with CKD. Diet can be very challenging for these individuals. Eating in excess can result in drastic changes to volume status, lead to the buildup of waste products from protein degradation, and cause electrolyte imbalances including changes in sodium, hyperkalemia, and hyperphosphatemia. Eating too little can lead to anorexia, muscle wasting, and malnutrition. This makes developing an optimal

diet vital for disease management. Dietary changes are initiated in patients with an eGFR of $<60 \text{ mL/min/1.73m}^2$. Certain dietary changes have been shown to slow disease progression and alleviate complications. Current dietary recommendations include protein restriction of $<0.8 \text{ g/kg}$, sodium intake $<2 \text{ g/day}$ for hypertensive, proteinuric, or volume overload patients, and potassium and phosphorus intake guided by lab values.

What is a plant-based diet?

A whole-food, plant-based diet is a diet centered on whole, unrefined, or minimally unrefined plants. This includes fruits, vegetables, starchy vegetables, whole grains, and legumes.

Existing research

Protein source and GFR progression

While existing data shows that protein amount can affect GFR progression, fewer studies look into how the source of protein affects GFR's progression. One study showed that higher red meat intake increased the risk of CKD progression to ESRD.¹⁸ An 11 year prospective cohort study done by Knight et al. looked at how different protein sources over time affected renal function and decline in individuals with normal and mild renal insufficiency. 1,642 women, aged 42-68, who were participants in the Nurses' Health Study gave blood samples in 1989 and 2000. They were also using semi-quantitative food

frequency questionnaires that were able to determine protein intake and by what source. Women with normal renal function, which was defined as $\text{GFR} > 80 \text{ mL/min/1.73m}^2$, showed no association with increased protein intake, regardless of the source, and renal function decline. However, women with mild renal insufficiency, defined as a GFR within $55\text{-}80 \text{ mL/min/1.73m}^2$, a significant association was found between protein intake and GFR decline. For every 10g increase in total intake, GFR declined by -1.69 mL/min ([CI], -2.93 to -0.45). Further, higher intake in animal protein resulted in an even greater decline by -1.21 mL/min ([CI], -2.34 to -0.33).¹⁹ High protein intake, in particular high animal protein consumption, was associated with acceleration in renal function decline in women with mild renal insufficiency.

A prospective, randomized, controlled trial was done by Garneata et al. to compare a conventional low-protein diet with a vegetarian low-protein diet supplemented with ketoanalogues. The adult patients had stage 4 CKD and ACR of $< 1000 \text{ mg/g}$. 207 patients were randomly assigned to a group receiving 0.3g/kg/day of vegetable protein with ketoanalogue supplementation or a conventional low protein diet of 0.6g/kg/day of protein from other sources for 18 months. Patients in both groups received nutritional counseling and monthly monitoring. Measured parameters included the need for renal replacement therapy or $>50\%$ decline in eGFR. GFR was measured monthly. Of the 207 individuals, 55 reached the measured end-points. Of this 28%, 42% were in the conventional low-protein diet, while only 13% from the low vegetable protein ($P < 0.001$).²⁰ Upon Kaplan-Meier analysis, the cumulative probability to reach one of

these endpoints was 12% for the vegetable protein group, compared to 33% for the conventional protein group.²⁰ The median eGFR was similar in both diet groups at any time during the 15 months, however, at the end of the study the vegetable protein group showed a slower decline in eGFR overall. This suggested that a vegetable based protein diet with supplemental ketoanalogue could slow CKD progression and delay the need for dialysis.

Soy protein for treating albuminuria

Treating albuminuria has been shown to slow the progression of chronic kidney disease, which makes this another target for dietary intervention. One way this has been done is by protein moderation, which has been shown to reduce proteinuria. However, there are a few studies that show certain protein sources, specifically soy-based protein sources from plants, can further reduce albuminuria in CKD patients. Further, one study showed that a diet high in animal fat intake and two or more servings of red meat per week may increase the risk for microalbuminuria²¹, while another study showed a diet high in whole grains, fruits and vegetables was shown to be associated with lower albuminuria.²²

Teixeira et al. performed a 7-month crossover study design with 34 individuals with type 2 diabetes mellitus, age 53-73 years, with albuminuria <2000 mg/24-h. In this study subjects served as their own controls. Individuals would consume a diet consisting of 0.5g/kg/day of either soy or casein protein for 8-week time periods, while all underwent a 4-week washout period of a 1.0g/kg/day diet of non-soy protein. Subject met with

registered dieticians every 2 weeks during the study to receive their protein powder isolate and review diet journals. Measured outcomes included urine albumin to creatinine ratio, LDL-cholesterol, HDL-cholesterol, and creatinine clearance. This study found significant reduction in ACR for the soy protein group (212.6 ± 139.6 versus 192.3 ± 122.7 , $P < 0.0001$), while the casein group found an increase in ACR (146.4 ± 88.8 versus 182.4 ± 102.2 , $P = 0.0020$).²³ Changes in CrCl were found to be not significant in both groups. This study concluded that soy protein versus casein protein significantly reduced albuminuria in patients with type 2 diabetic nephropathy.

Another study by Azadbakht et al. did a similar crossover, randomized clinical trial on 14 patients (10 men, 4 women) with type 2 diabetes with nephropathy. All the subjects had proteinuria ranging from 300-1000 mg/g, creatinine between 1-2.5 mg/dL, and a BUN between 20-40 mg/dL. Patients followed a diet of 0.8g/kg/day of 70% animal protein and 30% plant protein for 7 weeks, underwent a 4-week washout period, and then consumed a diet consisting of 0.8g/kg/day of 35% soy protein, 30% vegetable protein, and 30% animal protein. The study resulted in significant reductions in proteinuria and BUN ($P < 0.001$), as well as total cholesterol ($P < 0.01$) and triglycerides ($P < 0.02$), thus concluding a diet consisting of soy and plant protein can improve kidney function in patients with diabetic nephropathy.²⁴ Azadbakht et al. followed this study up with a randomized, clinical trial among 41 diabetic patients with nephropathy. The inclusion criteria was the same as the previous trial, only this time patients followed the two diets for 4 years total. Parameters were measured at baseline, and at the end of each year. A

significant reduction in proteinuria was seen in the soy protein group (667 ± 58 versus 513 ± 39 , $P<0.01$), while the animal protein group saw an increase in proteinuria (691 ± 71 versus 725 ± 81 , $P=0.1$).²⁵ While GFR was preserved and remained stable, it did so in both groups and was found not to be significant. A significant change was also found in fasting blood glucose levels in the soy group (141 ± 55 versus 121 ± 42 , $P<0.03$) and total cholesterol (255 ± 48 versus 201 ± 5 , $P<0.01$), while both outcomes increased in the animal protein group. The conclusion was made that longitudinal soy protein consumption improved indexes of kidney injury, provided better blood glucose control, and reduced cardiovascular risk better than an animal protein diet.

Fruits and vegetables for treating metabolic acidosis

As mentioned above, the presence of a metabolic acidosis in CKD patients has been shown to cause a more rapid decline in GFR and is associated with higher mortality, while treating this complication has been shown to slow disease progression. This makes metabolic acidosis an important target for dietary management for individuals with CKD. Current gold standard treatment is initiating sodium bicarbonate therapy when serum bicarbonate falls <22 mEq/L. However, this added dietary sodium may worsen hypertension and make volume control more difficult. Further adding to the problem is that current societal diets are high in acid-producing foods, including meats and processed foods. Two studies were done to see how a diet focused more on base-producing foods like fruits and vegetables would affect metabolic acidosis. These two

studies (all done by Goraya et al.) were randomized, controlled studies on individuals with different stages of hypertension-associated nephropathy.

The first study was done on 76 individuals with CKD stage 4 hypertension-associated nephropathy. Other inclusion criteria included having a plasma bicarbonate <22 mM, serum potassium of <4.6 mEq/L, non-malignant hypertension, no diabetes or cardiovascular disease, and 18 years of age or older. Individuals underwent a 6-month blood pressure control reduction protocol with an end goal of systolic blood pressure <140 mmHg. Of the 76, 35 received oral sodium citrate at 1.0 mEq/kg/day, while the other 36 received fruits and vegetables, free of charge from a food bank. Measured outcomes included urine net acid excretion, plasma bicarbonate, serum potassium, urine albumin, systolic blood pressure, and potential renal acid load. These were measured at baseline and one year. Plasma bicarbonate was higher in the HCO_3 group (21.2 ± 1.3 versus 19.5 ± 1.5 , $P < 0.01$) and the F+V group (19.9 ± 1.7 versus 19.3 ± 1.9 , $P < 0.01$). Systolic blood pressure was lower in the F+V group (131.7 ± 3.3 versus 136.3 ± 4.8 , $P < 0.01$), but not the HCO_3 group (136.0 ± 4.4 versus 136.1 ± 4.7 , $P = 0.88$). Potential renal acid load was also much lower in the F+V group (39.6 ± 10.4 versus 62.1 ± 6.8 , $P < 0.01$), while unchanged in the HCO_3 (59.3 ± 6.3 versus 59.0 ± 6.5 , $P = 0.28$).²⁶ The serum potassium levels remain unchanged for both groups from baseline and did not induce hyperkalemia. Baseline value for urine albumin were not different for both groups, and 1-year compared with baseline was lower for both groups ($P < 0.01$). This study was able to conclude that one year of dietary acid reduction using fruits and vegetables was able to improve

metabolic acidosis, reduce kidney injury, did not induce hyperkalemia, while reducing systolic blood pressure.

The second study conducted similarly compared F+V to oral sodium bicarbonate for treating metabolic acidosis, while also exploring its affect on GFR, urinary indices of kidney injury, and urinary angiotensinogen levels. This study had 108 individuals, all with CKD stage 3 hypertension-associated nephropathy. Other inclusion criteria included a serum bicarbonate of 22-24 mM, presence of macroalbuminuria, nonsmokers, and no cardiovascular disease or diabetes. Patients were divided into 3 groups. Group 1 received F+V prescribed by a registered dietician, group 2 received oral sodium bicarbonate at a dose of 0.3 mEq/kg/day, while group 3 received no treatment based on current care guidelines. Measured outcomes included plasma bicarbonate, serum potassium, blood pressure, urine albumin to creatinine ratio, urine angiotensinogen II to creatinine ratio, cystatin-C eGFR, and creatinine eGFR. Outcomes were measured at baseline and 36 months. The serum bicarbonate was higher in the F+V group (23.9 ± 0.6 versus 23.0 ± 0.5 , $P<0.001$) and in the oral sodium bicarbonate group (23.1 ± 0.6 versus 24.0 ± 0.6 , $P<0.001$), while decreasing in the usual care group. The F+V group and alkali therapy group both had significant preservation in eGFR progression when compared to the usual care group.

Measured Outcomes	Usual Care	Fruits and Vegetables	Oral Sodium Bicarbonate	P-Value: 3 Groups	Usual Care	Fruits and Vegetables	Oral Sodium Bicarbonate	P-Value: 3 Groups
Creatinine	42.6±7.6	42.3±7.1	42.6±7.0	0.99	28.8±7.3	36.9±3.7	35.2±6.9	<0.01

eGFR								
Cystatin-C	39.5±.8	39.4±6.4	39.6±6.6	0.99	26.6±7.0	34.3±6.4	32.7±6.7	<0.01
eGFR								

As in the previous study, the F+V group was the only group with significant blood pressure reduction (165.1 ± 10.1 versus 135.7 ± 4.5 , $P < 0.001$). All groups showed a decline in ACR, with F+V having the biggest decrease (318 ± 71 versus 242 ± 56 , $P < 0.01$), followed by the oral bicarbonate group (317 ± 72 versus 262 ± 62 , $P < 0.01$). Urinary angiotensinogen II levels also decreased in both the F+V group (35.5 ± 5.4 versus 32.1 ± 5.2 , $P < 0.01$) and oral bicarbonate group (35.4 ± 5.7 versus 32.0 ± 5.3 , $P < 0.01$), but not the usual care group.²⁷ This study was able to conclude that 3 years of dietary acid reduction with fruits and vegetables improved metabolic acidosis, reduced systolic blood pressure, reduced urinary kidney injury, and preserved eGFR in CKD stage 3 patients. The data also demonstrates F+V are effective in mitigating AII's contribution to nephropathy.

Plant protein and the treatment of hyperphosphatemia

As CKD advances, phosphate levels rise in the blood as the kidney is unable to filter out the excess phosphate ions. These patients begin to develop hyperphosphatemia, which increases a patient's risk for cardiovascular disease and fractures.^{28,29} Current treatment is guided by patient specific lab values. Because of the implications this complication has on quality of life and survival, diet has potential value as a form of management. Current

dietary recommendations are <800 mg/d of phosphorus in the diet. Plant-based foods are known to have less bioavailable phosphorus than meat, making a vegan diet particularly beneficial in this situation. Moe et al. conducted a crossover study on 9 patients with an eGFR of 25-40 mL/min/1.73m². These patients also had a normal serum phosphorus levels and were not on any phosphate binding medications. Patients were randomized to receive a diet of grain and soy based protein or animal and dairy based protein for 1 week. Each diet consisted of 20% protein and 800 mg of phosphorus. Patients consumed each diet for 1 week, underwent a 4 week washout period, and then consumed the opposing diet. Blood and urine measurements were taken at baseline and the end of each of the two test weeks. Outcomes measured included plasma phosphorus, plasma FGF23, and urine 24-h phosphorus excretion. The grain protein diet saw a statistically significant decrease in serum phosphorus (3.5±0.6 versus 3.2±0.5, P<0.02) and serum FGF23 (84±65 versus 61±35, P<0.008) compared to the meat/dairy protein diet, which saw a rise in both phosphorus (3.5±0.6 versus 3.7±0.6) and FGF23 (72±39 versus 101±83). The grain protein group also saw a decrease in urinary phosphorus excretion, however, it was not found to be a significant decrease when compared to the animal protein group (778±190 versus 416±233, P<0.07).³⁰ This study concluded that a plant-based protein source can have a different effect on phosphorus homeostasis compared to animal-based protein when managing CKD patients.

Moorthi et al. followed this study up with a 6-week long controlled trial on 13 individuals (7 female, 6 male), with an eGFR between 15-60 mL/min/1.73m². The other

inclusion criteria was similar to the previous study. Patients were instructed to consume their regular diet for 2 weeks, at which point they gave blood and urine samples which was used as baseline data. The participants were then provided a diet consisting of 0.84g/kg/day of protein (70% from plant sources, 30% from meat/dairy) and 0.8-1.0g/kg/day of phosphorus. Subjects met weekly to pick up prepared meals and meet with a dietician to discuss compliance and receive dietary education. At the conclusion of the 4 weeks, urine and blood samples were taken again, assessing serum phosphorus and FGF23 and 24-h urinary phosphorus. The result showed a significant decrease in urinary phosphate excretion (830 ± 224 versus 597 ± 233 , $P<0.001$).³¹ There was also a decrease in serum phosphorus and FGF23, but this decrease was not found to be statistically significant. This demonstrated a diet containing 70% protein from plant source is an effective way of lowering urinary phosphorus excretion, thus providing a potential alternative phosphate binding drugs.

Plant protein and all-cause mortality in chronic kidney disease

Plant protein sources and a plant-based diet has been shown to preserve GFR, reduce proteinuria, treat metabolic acidosis, and reduce serum phosphorus levels in patients with CKD. This type of diet has also shown to improve serum lipid levels, reduce blood pressure, and provide blood glucose control, which are all additional risk factors for CKD progression. Chen et al. did an observational study that looked at plant protein intake and its association with all cause mortality in chronic kidney disease patients. This

observational study looked at 14,866 patients from the NHANES III who were 20 years or older. During this NHANES III survey, patients underwent dietary interviews assessments which looked at how much of the participants diet was derived from plant or animal sources. This observational study included all the participants who had no dietary data missing. The subjects were stratified into two groups based of eGFR, group 1 being $>60 \text{ mL/min/1.73m}^2$, while group 2 was $<60 \text{ mL/min/1.73m}^2$. Participants were adjusted for age, sex, race, smoking history, physical activity, and caloric intake. The data showed that every 33% increase in plant protein ratio intake had a statistically not significant risk for death in the eGFR >60 group (HR, 0.87; [CI], 0.74-1.03), while the eGFR <60 group showed a significant lower risk for death (HR, 0.81; [CI], 0.66-0.99).³² When these groups were further adjusted for body mass index, hypertension, stroke, diabetes, myocardial infarction, and congestive heart failure there was an even stronger association with increased plant protein intake ratio and lower mortality in the eGFR <60 group. This suggests that for a given protein intake, higher proportion of plant sources is associated with lower mortality in CKD patients.³²

METHODS

Study design

The study is a 36-month randomized-controlled trial comparing the conventional recommended diet versus a plant-based diet for patients with chronic kidney disease. Individuals with CKD stage 3 (eGFR 30-59 mL/min/1.73m²) will randomly be assigned to receive a traditional diet prescribed for CKD patients, or a plant-based diet. The specifics of each diet will be discussed below. The primary outcome measured will be change in eGFR. Secondary outcomes being measured will include urine albumin, serum bicarbonate, serum phosphorus, and need for dialysis.

Study population and sampling

Patients participating in this study will be chosen from Boston Medical Center outpatient nephrology clinics. These individuals will be selected based off the inclusion and exclusion criteria that will be outlined below. After patients are selected they will continue to resume their usual routine medical care at their respective outpatient clinics. After looking at a previous study that showed a meaningful change in GFR over time to be -4.8 ± 3.7 mL/min/1.73m² was associated with increased mortality³³, it was determined that a sample size of 40 in each group, using a t-test sample size calculation, was needed to achieve an 80% power and an alpha of 0.05 to detect a $\geq 50\%$ reduction in the change in GFR over time. This study will aim for a sample size of 50 to allow for a potential 25% dropout rate over the 36 months.

Study subjects will be chosen based off the following inclusion criteria: (1) CKD stage 3 with an eGFR of 30-59 mL/min/1.73m²; (2) history of hypertension that is currently well controlled as evidence by a systolic blood pressure <150 mmHg; (3) history of non-insulin dependent type 2 diabetes mellitus that is currently well controlled as evidence by a hemoglobin A1c <9%; (4) urine albumin-to-creatinine ratio of 30-1000 mg/g; (5) a decline in GFR >4.8 mL/min/1.73m² in the previous year; (6) metabolic acidosis defined as a serum bicarbonate >22 mEq but <24 mEq and not taking oral sodium based alkali therapy; (7) serum phosphorus levels >4.0 mg/dL but <4.5 mg/dL and not taking phosphate binders; (8) nonsmokers based off no tobacco use for over one year; (9) no hospitalizations related to chronic kidney disease for the previous year leading up to the study; (10) no history of cardiovascular disease; (11) ability to understand and follow through on the dietary interventions; and (12) >18 years of age but <65 years of age. Exclusion criteria include; (1) chronic kidney disease caused by any genetic disorders, congenital anomalies, autoimmune disease, glomerulonephritis, vascular disease, such as renal artery stenosis, primary glomerular disease, or tubulointerstitial disease; (2) history of cardiovascular disease, including previous stroke, myocardial infarction, or heart failure; (3) acute kidney injury within the previous year of the study; (4) plasma potassium >4.5 mEq/L; and (5) unable to tolerate a plant-based diet for either health or socioeconomic reasons.

Treatment (or intervention)

Subjects in this study will be randomly allocated into one of two groups. Subjects in group 1 will receive the conventional recommended diet for CKD patients, while subjects in group 2 will receive a plant-based diet. Both diets will be isocaloric at 35 kcal/kg/day. Of the caloric intake, 60% will be from carbohydrates, 30% from fats, and 10% from protein. Each diet will provide 0.8 g/kg/day of protein, 0.8-1.0 mg/kg/day of phosphorus, <3 g of potassium, and <2 g of sodium. The conventional diet will consist of animal and dairy sources for 70% of its protein, while the other 30% will come from plant sources. The plant-based diet will consist exclusively of whole grains, legumes, fruits, and vegetables.

Study variables and measures

The primary outcome being measured is change in glomerular filtration rate, which will be done using the CKD-EPI estimation equation because it has been shown to be just as accurate as the MDRD equation³⁴ and is more accurate for risk prediction of adverse outcomes for CKD patients.³⁵ This CKD-EPI equation utilizes serum creatinine, sex, race, age, and body surface adjustment to calculate GFR, however, a more accurate version of this equation can be used that makes use of another serum marker; cystatin C. The CKD-EPI combination equation using both serum creatinine and cystatin C has been shown to be more accurate in predicting GFR³⁶, therefore, this version of the equation

will be used in the study. Secondary outcomes that will be measured are urinary albumin levels, plasma bicarbonate and phosphorus, and need for dialysis.

Recruitment

Potential study participants will be recruited from Boston Medical Center outpatient nephrology clinics. Patients will be contacted to participate in this study in two ways. Some will be directly approached in the waiting rooms of outpatient clinics, explained the study and its design, and asked to give consent to review their electronic medical record to see if they fit the criteria to participate in the study. Other potential candidates will be contacted by telephone and will similarly be explained the study and asked for consent to evaluate the electronic medical record. After individuals are found to meet the inclusion and exclusion criteria, they will once again be contacted and asked to participate in the study. Once an individual agrees to both participation and randomization, they will be matched for baseline glomerular filtration and baseline urine albumin with another study subject and undergo randomization.

Data collection

Data will be collected at the Boston Medical Center laboratory located in the Shapiro Building. This will include both urine samples and blood draws. Baseline measurements will be collected on the first day of the trial before any dietary intervention has begun. The collections will be done after 8-hour fasting beginning the night prior. After initial

urine and blood samples are obtained, participants will then begin following their respective diets. The samples collected will be used to determine eGFR, urine albumin levels as a urine albumin-to-creatinine ratio, and serum bicarbonate and phosphorus. The same measurement tools, assays, and lab will be used to obtain the data for each sample collected. Samples will then be collected every 4 months, \pm 1 week to allow for patient convenience, in a similar fashion for the 36 months of the study, equating to a total of 10 lab visits per participant for the duration of the trial. After the final measurements are calculated, the data will be transferred into an Excel document that will keep track of each individual's data. At the conclusion of the trial, this compiled data will be used to perform the statistical analyses discussed below.

Data analysis

Subject characteristics at the beginning of the study, including age, race, sex, eGFR, albumin-to-creatinine ratio, serum bicarbonate, and serum phosphorus, will be tabulated by mean and standard deviation. A t-test will be done to compare baseline characteristics between the two groups. The primary outcome being measured is change in eGFR. Secondary outcomes being measured include urine albumin levels, serum bicarbonate, and serum phosphorus. The changes from baseline to the conclusion of the trial will be described as mean and standard deviations and compared using a t-test. In order to evaluate other variables that may be related to the primary outcome, multivariate analysis will be done to adjust for age, race, and sex. Stratified analysis will also be done to

control for any factors determined to be confounding. A P-value <0.05 indicates statistical significance. Graphs will be included to give a visual representation of the data.

Timeline and resources

During the initial recruitment phase of the trial, both physicians and medical or physician assistant students will review the electronic medical records and contact potential candidates for the trial based on the inclusion and exclusion criteria discussed above.

After participants give consent to be in the study, they will have two follow-up appointments to attend. The first will be with one of the primary co-investigators of the study, a nephrology physician at Boston Medical Center. This physician will go over specific aims and details of the trial with the participants individually and answer all questions. After this meeting, the subject may resume seeing their respective nephrologists in the BMC system, who will all be aware of the trial that is taking place.

The second appointment participants will attend is with a registered dietician with a specialization in kidney disease. Here they will receive education on the particular diet they have been randomized too. Participants will also receive a food diary, where they will record when and what they eat. Participants in both groups will receive food stamps that will allow them to pickup fresh produce, free of charge, at participating community food banks. This will provide the 30% of plant-sourced protein for the conventional diet group, while providing the same amount of produce for the plant-based group.

After the conclusion of these two appointments participants will then schedule a time to have their baseline urine samples and blood draws done. After the completion of the labs, patients will begin their respected diets that same day. Subjects will record in their food journals daily, and meet with the renal dietician monthly to review them, have questions answered, and ensure diets are being followed. Participants will also follow-up with their nephrologists every 4-6 months as part of their routine care. Patients will have lab data obtained every 4 months. This resulted data will be sent directly to a statistician who will manage the Excel document. A group of unblinded statisticians will perform interim analysis comparing both groups as a measure of safety to make certain neither group is being put at unnecessary risk. At 36 months final data will be gathered and the trial will be complete.

Institutional Review Board

An application detailing the protocol of the study will be submitted for full review to the Boston University Medical Campus Institutional Review Board. IRB approval will be obtained prior to the recruitment of study participants.

CONCLUSION

Discussion

This study would be the first of its kind that compared a conventional CKD diet with a completely plant-based diet that looked at glomerular filtration rate as the primary outcome. Previous studies that have been done that looked at plant-sourced food and CKD have either been observational studies, control trials that used study subjects as their own controls, or looked at other measured parameters as the primary outcome. This study also has strengths in the population being sampled by taking patients with the most prevalent stage of chronic kidney disease, and those with the two most common comorbidities.

While this study does have strengths, there are still notable limitations. The sample size is small, and would need to be studied on a larger scale to further validate the results. This study also only addresses one stage of chronic kidney disease, and it will still remain unknown if this diet may provide the same potential benefits or harm at earlier and later stages of the disease course. The smaller sample size and specific inclusion and exclusion criteria may limit the generalizability of the study, specifically for those with different comorbidities, past medical history, and patients at higher risk of adverse outcomes.

Additionally, this study has several anticipated obstacles. The dietary interventions being studied require strict adherence to prove the results. Adopting a new diet can be very challenging for patients and requires lots of modification to their

previous lifestyle. This alone may cause patients to exit the trial. The study also calls for close and regular follow-up. This could become very time consuming for participants, and may even result in patients leaving the trial as well. If adopting either diet is found to be a big problem for patients, they may need further education on how to apply these changes to their daily lives.

Summary

While no optimal diet exists when managing patients with CKD, there are guidelines and recommendations that have become accepted by nephrologists. While some studies exist that support these guidelines, other studies have been done that demonstrated no benefit to these recommendations at all. Further, these current standards fail to address whether the source (plant versus animal) has any affect on chronic kidney disease.

The research above suggests that a plant-based diet may have an overall positive effect on several parameters used to assess the severity, prognosis, and risk of mortality for patients with chronic kidney disease. This includes reducing albuminuria as a sign of kidney injury, treating metabolic acidosis, managing electrolyte abnormalities such as hyperkalemia and hyperphosphatemia, and recuing all-cause mortality. Further, this type of diet may also aid in blood pressure lowering and blood glucose control, which are both integral parts of CKD management. Most importantly, a plant-based diet may actually slow the progression of chronic kidney disease by delaying the decline in GFR.

The proposed study design will compare a plant-based diet with a conventional diet and its affect on the glomerular filtration rate over time in patients with chronic kidney disease. This may help identify any gaps that exists in current dietary recommendations, and may even shift how patients with CKD are educated on the food they consume on a daily basis. This study could demonstrate how the source of food, rather than amount, can impact patients with chronic kidney disease.

Clinical and/or public health significance

For patients with chronic kidney disease, there is no cure. Current management is aimed at slowing the rate of GFR decline, treating associated comorbidities, and addressing complications as they arise. Recommendations are also made regarding lifestyle modifications, specifically diet. If a plant-based diet is found to delay the progression of chronic kidney disease while improving additional disease complications, patients may see an overall improvement in quality of life and reduction in symptoms that affect their daily lives. This would also potentially reduce the amount of medications they need to take, as well as delaying the time to dialysis or renal replacement therapy. Individual patients would not be the only ones benefitting from this diet. The healthcare costs for patients with chronic kidney disease may show a decline as well, especially if the time to dialysis and need for medications is delayed. Overall, adopting a plant-based dietary lifestyle may become something that patients with chronic kidney disease can do each day in order manage their disease, slow its progression, and improve their quality of life.

LIST OF JOURNAL ABBREVIATIONS

AJCN	American Journal of Clinical Nutrition
AJKD	American Journal of Kidney Disease
BMJ	The British Medical Journal
Circ	Circulation
CJASN	Clinical Journal of the American Society of Nephrology
DC	Diabetes Care
JAMA	The Journal of the American Medical Association
JN	Journal of Nutrition
JRN	Journal of Renal Nutrition
KI	Kidney International
NDT	Nephrology Dialysis Transplantation

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CURRICULUM VITAE



