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The role of diet therapy in chronic kidney disease

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Thesis

THE ROLE OF DIET THERAPY IN CHRONIC KIDNEY DISEASE

by

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I’d like to thank my late father for being the inspiration behind this thesis. Without the impact you had on my life, I would not have been able to write this.

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ABSTRACT

Background

Chronic kidney disease (CKD) is a condition characterized by gradual loss of kidney function over time. Millions of adults have CKD and those who have diabetes, hypertension, and family history of kidney failure are at highest risk of its development. Patients may develop comorbidities, such as cardiovascular disease, anemia, mineral and bone disorders, and peripheral nervous system diseases. Those with kidney failure require dialysis or kidney transplantation, as well as medications, diet therapy, restriction of fluid intake, and lifestyle modifications. The cost for such treatment represents an enormous burden on healthcare systems worldwide, costing about 8% of the Medicare budget in the U.S.

Literature review findings

Chronic kidney disease is now described based on internationally accepted definitions and diagnosed, when structural or functional abnormalities of the kidneys persist for more than 3 months. End-stage kidney disease is the last stage of chronic kidney disease and is associated with a decreased quality of life and life expectancy. This comprehensive literature review focuses on the effectiveness of dietary therapy in delaying the progression of CKD to end stage kidney disease (ESKD). Current evidence provides guidelines to manage ESRD with the general population. However, despite this, many clinicians do not know how to use diet as part of clinical management.

Proposed methods

Given the broad spectrum of different dietary therapies to decelerate progression of CKD, many providers do not utilize this information in clinical practice. A workshop hosted by registered dieticians, summarizing the most up-to-date literature on the topic of dietary interventions to slow down CKD progression would be beneficial. The workshop will measure mid-level and high-level practitioner's knowledge on dietary therapy for CKD and assess this post-workshop. The goal is to expand the knowledge of providers and equip them with the resources necessary to educate patients on healthy dietary modifications, in order to minimize progressive CKD.

Conclusions

Despite the availability of dialysis and recent advancements in post-transplant care, there is a benefit to lifestyle modification. There is promising evidence that a diet low in protein, potassium, or salt and following certain diets, such as the Mediterranean diet, is beneficial in the deceleration of CKD to end stage renal disease (ESRD). A diet containing processed foods, high protein, high salt, and high potassium content has been associated with an increased risk of transition from late-stage CKD to ESRD. It is possible that these dietary recommendations may apply to prevention of CKD or ESRD. The workshop will present the most up-to-date knowledge in the area of dietary therapies for CKD. A curriculum for mid- and advanced-level health care providers will provide them with the tools necessary to provide their patients with nutrition and lifestyle management.

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LIST OF ABBREVIATIONS

AER…….Urinary Albumin Excretion Rate

ACE …….. Angiotensin-Converting Enzyme Inhibitors

AKI …….....……. Acute Kidney Injury

ARBs…… ……Angiotensin II-Receptor Blockers

CKD……..Chronic Kidney Disease

DCT ……... Distal Convoluted Tubule

eGFR……..Estimated Glomerular Filtration Rate

ESKD……Early Stage Kidney Disease

GFR……. Glomerular Filtration Rate

HPD……High Protein Diet

HSD……. High Salt Diet

KDIGO……. Kidney Disease: Improving Global Outcomes

LO…….Learning Objectives

LPD……. Low Protein Diet

LSD……. Low Salt Diet

MDRD…….. Modification of Diet in Renal Disease

NFK KDODI....National Kidney Foundation Kidney Disease Outcomes Quality Initiative

NP…….Nurse Practitioner

PA-C……..Physician Associate

PCP …… Primary Care Physicians

PCT ……. Proximal Convoluted Tubule

PEW …….... Protein Energy Wasting

RCT ……Random Control Trials

uACR ……Urine Albumin-to-Creatinine Ratio

USD…….. United States Dollars

WHO……. World Health Organization

INTRODUCTION

Background

As defined by the CDC National Kidney Foundation (NKD), chronic kidney disease, or CKD, is a condition characterized by a gradual loss of kidney function over time [iv]. The kidneys' main function are to maintain homeostasis by excreting and reabsorbing necessary substances, such as electrolytes, water, and maintaining acid-base balance via a sophisticated filtration system. As kidney disease progresses, the filtration system declines, and toxic levels of substances can accumulate in the blood. CKD is categorized into five stages of worsening severity (1-5). Early detection of CKD is performed through measuring the glomerular filtration rate (GFR) and proteinuria. As CKD progresses, other diseases, such as cardiovascular disease, anemia, or electrolyte, mineral, and bone abnormalities, can occur. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD), which includes diet therapy, restricted fluid intake, lifestyle modifications and dialysis or renal transplant therapy for end stage kidney failure. Nutritional and lifestyle modifications have been studied in the context of improving overall health and decreasing risk for illness, such as kidney disease.

Statement of the Problem

Chronic kidney disease (CKD) is an important public health concern in developed countries because of rising prevalence and high costs of care. The rise in prevalence may be due to preventative strategies not being implemented effectively. Furthermore, despite growing progression of this disease, there continue to be fewer preventative therapies available for CKD than other chronic diseases, such as cardiovascular disease. Healthy dietary habits, physical activity, and overall lifestyle contribute to our general health and help prevent illnesses, such as cardiovascular diseases or diabetes, which are risk factors for CKD. Preventative methods could include public health strategies to prevent risk factors for CKD, raising awareness of the rise in prevalence, implementing early at-risk screening, and improving dietary risk exposures within medical practices and practitioner education with patients, especially those at risk. Currently, research has shown that diet therapy and lifestyle modifications can be used to prevent the progression of CKD. However, there seems to be a limit in clinical practices providing dietary therapy as part of a patient's management and education.

Hypothesis

After a targeted workshop, clinicians will exhibit an improved knowledge in dietary interventions for chronic kidney disease

Objectives and specific aims

The objective of this thesis is to provide medical providers with the information necessary to educate patients on dietary and lifestyle changes to prevent the progress on chronic kidney disease. The study aims to:

- Identify specific diets that delay the progression of CKD
- Summarize current data on diet therapy that decrease risk of kidney disease
- Designing and implementing a workshop on most effect diet therapy and provide information to health care professions

REVIEW OF THE LITERATURE

Overview

Epidemiology

Kidney disease is the ninth leading cause of death in America. It accounts for close to 50,000 deaths annually. An estimated 37 million Americans have chronic kidney disease (CKD). The majority of patients with CKD are aged over 60 years due to aging degeneration in kidney function. The patients with stage 3b CKD and above are especially at high risk for progression to end stage kidney disease (ESKD), requiring dialysis or kidney transplant, in addition to cardiovascular events and death. [i] In the U.S alone, 786,000 people are living with ESKD with 71% on dialysis and 29% having had a kidney transplant. Men have a 50% greater risk for developing ESKD. [xiv]

Unfortunately, nearly 90% of those with CKD remain undiagnosed until it reaches a critical point, such as ESKD, since it is largely asymptomatic and there is little awareness about the importance of CKD testing and diagnosis among practitioners even for people at high-risk for CKD. [i] Common causes of CKD include diabetes mellitus and hypertension, which are highly prevalent in the general population. Diabetes is the most common cause of CKD worldwide, followed by hypertension. Diabetes can lead to glomerular hyperfiltration over time, which can cause significant accumulation of scar tissue within the kidney. These diseases are the leading causes of CKD in middle- and high-income countries worldwide, accounting for approximately 35% and 25% of kidney disease. [xiv]

In addition, the financial burden of CKD is substantial. Total Medicare expenditures in 2016 for kidney disease were >$114 billion, $79 billion across all CKD stages and $35 billion for ESKD, including dialysis and kidney transplants. [xiv] More than 450,000 people in the United States are presently undergoing dialysis for the treatment of kidney failure. More than 120,000 people are awaiting kidney transplantations in the United States with fewer than 17,000 receiving a new kidney each year. [i]

According to the United States Renal Data System 2020 Annual Data Report, in 2018, adjusted mortality among Medicare beneficiaries ages 66 years or older was more than twice as high among those with CKD (96.0 per 1,000) compared to those without CKD (41.0 per 1,000) (Figure 1).[xxii] Adjusted mortality decreased by nearly 15% in patients receiving hemodialysis and by nearly 20% in patients receiving peritoneal dialysis between 2009 and 2011. Adjusted mortality is significantly lower in patients with a kidney transplant (48.9 per 1,000) compared with patients receiving dialysis (160.8 per 1,000). Despite the multiple modalities for treating CKD and ESKD, there is still a lack of availability for all patients with this disease. Additionally, it is a great burden on the patient with the external stress factors of scheduling and adhering to appointments while maintaining employment, school, family obligations, and other social factors.

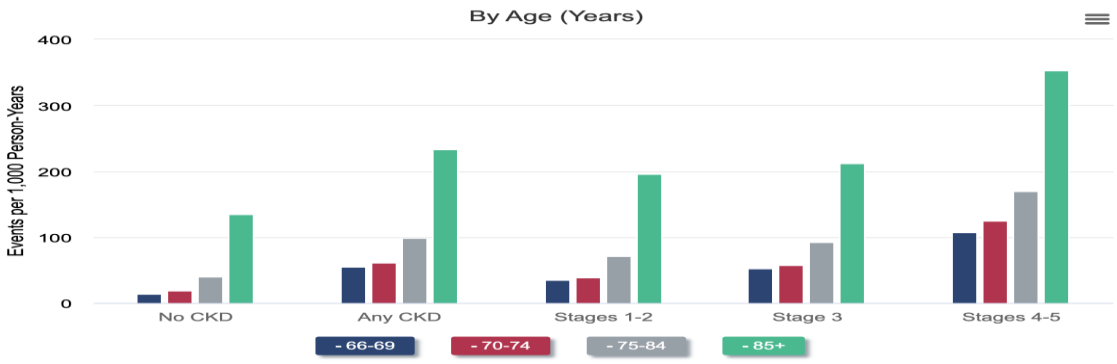

Figure 1: Adapted by the *USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020. "Adjusted all-cause mortality in Medicare beneficiaries aged ≥66 years, by CKD status and stage". [xxii]

Pathophysiology

Glomeruli

Chronic kidney disease is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min, persisting for 3 months or more (Figure 2). Glomerular filtration, normally between 120 to 125 ml/min, is the initial process in urine production. Glomerular filtration rate (GFR) is the volume of plasma that is filtered in a minute and depends on the total available surface area for filtration, net filtration pressure, and filtration membrane permeability with oncotic and hydrostatic pressure. The glomerulus is regulated intrinsically and extrinsically to maintain the GFR. The intrinsic control function adjusts its own resistance to blood flow, constricting and dilating the afferent and efferent arterioles depending on the concentration of sodium chloride within the renal tubules and or blood flow it senses. Extrinsic control maintains the GFR and also maintains the systemic blood pressure via the sympathetic nervous system and the renin-angiotensin-aldosterone mechanism. [xxi]

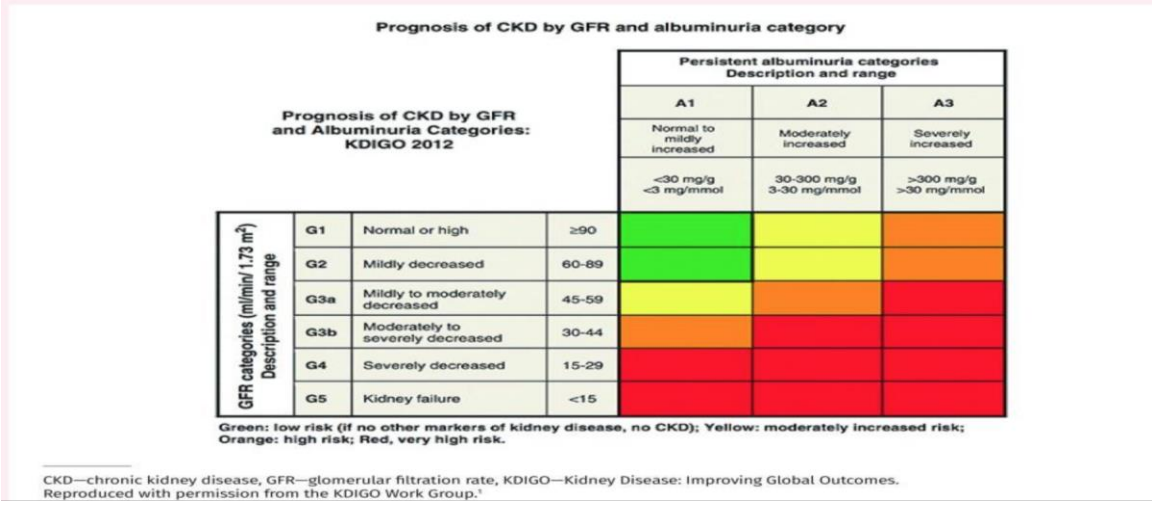

Figure 2: Adapted from the official Journal of The Transplantation Society, and the International Liver Transplantation Society. "Current CKD nomenclature used by KDIGO: Classification of CKD based on cause, GFR category, and albuminuria category."[vii]

Tubules

The nephrons filter, reabsorb, and secrete substances via the tubules. The tubules of the nephron are divided into four segments: the proximal convoluted tubule (PCT), the nephron loop, the distal convoluted tubule (DCT), and the collecting tube. Under normal circumstances, the PCT reabsorbs all the glucose and amino acids, as well as 65% of sodium and water. The nephron loop is divided into the descending and ascending limbs, where the descending limb functions to reabsorb water by osmosis via aquaporins. Then, in the ascending limb, sodium and solutes, such as potassium and chloride, get reabsorbed together through a symporter. The primary function of the DCT is active sodium transport and potassium secretion via aldosterone. It also reabsorbs calcium.

Finally, the final stage of reabsorption occurs along a collecting tubule. The reabsorptions that occur here include the final sodium and calcium reabsorption, as well urine concentration and anti-diuresis via anti-diuresis hormone (ADH).

Interstitium

Chronic and sustained injury from long term and progressive nephropathies develop into destruction of the kidney's normal architecture and evolve into progressive kidney fibrosis. This affects all the 3 compartments of the kidney, which is composed of the glomeruli, tubules, and interstitium. Histologically this evolves into glomerulosclerosis, tubulointerstitial fibrosis, and vascular sclerosis. CKD can also lead to structural changes of the urinary tract causing changes in the composition of the urine, reducing kidney function. [xviii] Kidney tissue in systemic diseases is injured by accelerated vascular damage, glomerular hypertension, and increased cellular glycosylation and oxidation. [xxiii] It is a state of progressive loss of kidney function ultimately resulting in the need for dialysis or transplantation.

Physiology

The kidneys have exocrine and endocrine functions regulating and maintaining life essential biological mechanisms in the body. The endocrine functions include the activation of vitamin D, so bones can absorb calcium, blood pressure regulation via hormone synthesis, and erythropoiesis which is the production of red blood cells.[xxi] Additionally, there is an intensified vascular risk that develops naturally over the course of CKD, where traditional risk factors, such as atherosclerotic or plaque accumulate in

the arteries, have a significantly bigger effect in early stages. [v] The exocrine functions involve fluid and electrochemistry homeostasis, metabolic regulation, and expelling body waste (Figure 3).[xvi] CKD interferes with the body's physiological and biological mechanisms, including the aforementioned endocrine and exocrine functions. [xxiii] An important regulatory system utilized by the kidneys is the renin-angiotensin-aldosterone system (RAAS). The RAAS system also regulates blood pressure, fluid balance, sodium and potassium, and a balance between inflammatory and anti-inflammatory effects.

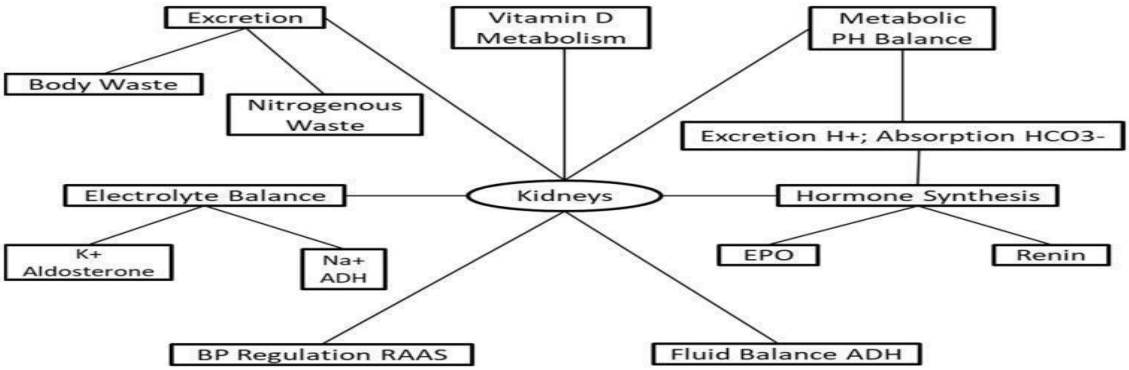

Figure 3: Adapted from Naber T et al., 2021 "The physiological functions of the kidney"

Clinical Course

Clinical management may improve CKD in stages 1-3b, if risk of advancement towards ESRD is differentiated from early CKD that is unlikely to progress. In stages 4 and above, symptoms of later stage CKD include fatigue, swelling around the eyes and/or ankles, foamy urine, ammonia smelling breath, nausea, vomiting, persistent itching with or without rash, difficulty sleeping, and shortness of breath. Many of these symptoms do not appear until later stages of CKD or until ESKD.

Many CKD patients are at risk of inappropriate electrolyte build-up, including hyperkalemia and hyperphosphatemia, but are also in harm of developing chronic metabolic acidosis, osteoporosis, hypertension, and fluid overload. These risks may be minimized and the disease's progression may be slowed through careful monitoring of protein, phosphorus, potassium, sodium, and calcium, relieving symptoms experienced by CKD patients. [xvi] As the disease progresses, patients have a more restrictive diet. There is an increased nutritional sensitivity due to the decreased filtration; for example, the inability to excrete sodium results in water retention or edema and can cause hypertension. Elevated potassium can cause deep tendon reflex abnormalities, cardiac problems, and gastrointestinal disturbances.

Treatment

Most patients with CKD that are managed in primary care are categorized in stage 3, further subdivided into 3a and 3b (eGFR of 30 to 59 mL/min per 1.73 m^2) with the latter portending a higher likelihood for progression of disease categories. Patients who have more advanced CKD (eGFR of < 30 mL/min per 1.73 m^2) fall into stage 4 or 5 CKD and are usually managed in consultation with a nephrologist. There are multiple ways to treat CKD; in the early stages, diet, hypertension and diabetes control, and avoidance of tobacco are important. At CKD stage 4, it is important to educate patients about kidney replacement therapy, which includes hemodialysis, peritoneal dialysis, and kidney transplant. In early stage (1-3) and pre-dialysis CKD, treatment with lipid-lowering agents, such as statins, reduced the risk for cardiovascular events, in spite of a weaker association between low-density lipoprotein cholesterol (LDL-C) and patient

outcomes in stages 3 through 5. [xxiv] The strongest evidence of treatment benefit in patients with early CKD is from randomized control trials (RCTs) of SGLT2 inhibitors, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II-receptor blockers (ARBs). However, these studies focused on patients with proteinuric diabetic kidney disease and the data to support the use of these agents for other causes of CKD are weaker. [xxiv] The current mainstay of CKD therapy is renin–angiotensin system (RAS) blockade using angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs). However, RAS blockade is indicated only in proteinuric or hypertensive nephropathies and only delays, not prevents, CKD progression. [xx] Both ACE inhibitors and ARBs slow CKD progression in proteinuric kidney diseases. Steroidal drugs, such as spironolactone or eplerenone, and nonsteroidal drugs, such as finerenone, also have an antiproteinuric effect but whether they delay CKD progression when used in combination with ACE inhibitors or ARBs remains to be proven. [xix] No current therapy can prevent acute kidney injury (AKI) or the AKI-to-CKD transition.

Based on the Wagner Chronic Care Model, the prevailing care strategy for CKD should consist of three phases. One phase included reducing vascular risk factors in primary care during early disease, including lifestyle modifications such as smoking cessation, dietary changes, exercising, blood pressure, glycemic and lipid control, and periodic monitoring of kidney health). Another phase included managing comorbidities that develop in progressive cases including, anemia and bone diseases. The last phase included multi-professional, intensive care for patients transitioning to renal replacement therapy. [xxiv] For all CKD patients, primary care physicians (PCPs) should check for

causative agents such as medicine interactions that might cause acute kidney injury or toxic build up on other medications.

Dialysis is utilized for more progressive CKD, stage 5 (GFR <10 ml/min per 1.73 m) which is clinically symptomatic. According to the National Kidney Foundation, the average life expectancy on dialysis is 5 to 10 years. Dialysis removes waste, salt, and extra water to prevent build up in the body, achieving a safe level of nutrients and chemicals in the blood, and helps control blood pressure. There are two types of dialysis, peritoneal and hemodialysis. Hemodialysis utilizes an artificial kidney (hemodialyzer) to remove waste, extra chemicals, and fluid from the person's blood through a fistula, catheter, or graft access. Treatment typically occurs three times a week for a few hours a day. This can be time consuming and difficult for people to manage. Peritoneal dialysis, when blood is cleaned inside the body, utilizes a catheter placed surgically into the abdomen to make an access. During the treatment, the abdominal area is slowly filled with dialysate through the catheter. The blood remains in the arteries and veins that line the peritoneal cavity. Extra fluid and waste products are drawn out of blood and into the dialysate. There are two major kinds of peritoneal dialysis, automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD). CAPD is performed without machines and is self-managed. Patients must be disciplined to ensure they do their treatment three to four times per day. APD is also performed at home but using a special machine called a cycler. It is usually done at night while patients are asleep because each cycle lasts one to one and a half hours. Although there are many options,

dialysis is not a curative treatment and is not a long-term solution for those with CKD. Once started, patients must continue until they are able to undergo transplant surgery.

Testing

Early-stage CKD is often asymptomatic, making laboratory testing imperative for at-risk patients. Annual GFR monitoring is recommended in adults who are taking medicines that can adversely affect kidney function. These medications include calcineurin inhibitors, lithium, or chronic use of non-steroidal anti-inflammatory drugs. Additionally, testing should be offered to adults with the following risk factors: diabetes, hypertension, previous episode of acute kidney injury, cardiovascular disease, structural renal tract disease, recurrent renal calculi, prostatic hypertrophy, multisystem diseases with potential kidney involvement, gout, family history of end-stage kidney disease (GFR category G5), hereditary kidney disease, or incidental detection of hematuria (blood in urine) or proteinuria (protein in urine).

Diagnosis uses two accessible and inexpensive lab tests. The first test is serum creatinine with eGFR, a test of kidney function. The second is urine albumin-to-creatinine ratio (uACR), a test of kidney damage. While eGFR results are common within metabolic laboratory panels, the test alone is insufficient for CKD detection. Albuminuria, when high concentrations of the protein albumin leads to its detection in urine, reflects endothelial or tissue inflammation that may cause proximal tubular damage. The proximal tubules are a key absorption site within the kidneys, so this reflects progressive loss of function. [i] Both tests should be performed at least annually for at-risk patients by primary care practitioners (PCPs) and clinicians that manage diabetes

and hypertension, such as cardiologists and endocrinologists. The majority of patients with CKD are seen in a primary care setting. The role of PCPs is crucial in improving CKD care by engaging in diagnosis and management as early as possible in order to slow progression and prevent cardiovascular and kidney complications.

Existing Research

Protein

Diet modification has been studied in the context of CKD management and treatment. It has been found to be associated not only with a delay in developing CKD but also with a decreased risk of death from various comorbidities, especially those that are cardiovascular related. The current recommendations by the NKI KDOQI for nutritional requirements in adult patients with non-dialysis CKD stages 3-5 are 0.55-0.6 g/kg/day (ND-CKD) and 0.8 g/kg/day for kidney transplant recipients (Table 1). [xii]

	ND-CKD stage 3–5	Transplantation
Energy (kcal/kg ideal weight/day)[a]	25–35	25–35 in maintenance KTR 25 (obesity) 35–40 for the first 4 weeks after transplantation
Protein (g/kg/day)[a,b]	0.55–0.60 or 0.28–0.43 plus keto/amino acid supplementation	0.8
	0.80–0.90 (diabetes)	0.6–0.8 (CKD stages 3–5 T)
	1.0 (illness)	≥1.4 (for the first 4 weeks after transplantation or if high doses of prednisone is required)
Sodium (g/day)	<2.3	<2.3
Potassium[c]	Adjust dietary potassium intake to maintain serum potassium within the normal range	Adjust dietary potassium intake to maintain serum potassium within the normal range
Calcium (mg/day)	800–1,000[d]	Insufficient data to define optimal dietary calcium intake in KTR (research priority)
Phosphorus[e]	Adjust dietary phosphorus intake to maintain serum phosphate levels in the normal range	Adjust dietary phosphorus intake to maintain serum phosphate levels in the normal range
Fiber (g/day)	25–38	25–38
Vitamin D (IU/day)	600–800	600–800
Vitamin B12 (μg/day)[f]	2.4	2.4
Folic acid (μg/day)[f]	400	400
Vitamin C (mg/day)[f]	90 (M), 75 (W)	90 (M), 75 (W)
Vitamin E (mg/day)[f]	15	15
Vitamin K (μg/day)[f]	120 (M), 90 (W)	120 (M), 90 (W)
Selenium (μg/day)[f]	55	55
Zinc (mg/day)[f]	11 (M), 8 (W)	11 (M), 8 (W)

Table 1: Adapted from Ikizler et al., 2020 American Journal of Kidney Disease: The KDOQI Clinical Guideline for Nutrition in CKD: 2020 Update. [xii]

One prospective study, Naber et al., 2021, found that high protein diets (HPD) caused glomerular hyperfiltration, engorged blood vessels, and decreased oncotic pressure, resulting in vasodilation of the afferent arteriole. HPDs contributed to developing glomerular damage, which, combined with the renal decline from diseased kidneys contribute to CKD acceleration. [xvii] Whereas, a low protein diet (LPD) showed improvement in hyperfiltration, lower byproduct waste, and decreased glomerular pressure causing easier renal workload. Proteinuria, a diagnostic marker for CKD, declined by 20–50% in CKD patients who adhered to a low protein diet in the Naber et al., 2021 study. Although low protein diets provided many advantages to CKD patients,

medical providers raised concerns about this study, mainly in regard to protein-energy undernutrition and protein-energy wasting (PEW) in CKD patients because of insufficient energy consumption. However, the benefits of LPD were also supported in another study, Molina et al., 2021. The study found a beneficial effect of protein restriction and on quality of life demonstrating that protein restriction presented significantly higher scores for general health and state physical compared to the control group.[xv]

Another study, the Modification of Diet in Renal Disease (MDRD) study, found proteinuria to be one of the two strongest predictors in the rate of CKD progression. Furthermore, this study also found that the progression of kidney disease only minimally decelerated with an LPD. However, the study had several relevant limitations, such as the relatively small sample and short follow-up time. [viii] The MDRD study also found effects of a LPD and low sodium diet (LSD) on the afferent arteriole. Short term, lower intake of dietary protein led to greater constriction of the afferent arteriole. Thus, LPD resulted in incremental reductions in the glomerular filtration rate, which lead to less glomerular hyperfiltration, but, chronically, a sustained LPD has been found to diminish glomerular damage and stabilize or improve function. [viii] A randomized controlled trial found that the renal protective effects of a low-protein diet can be synergistic with the direct effect of a low-sodium diet, as well as with the effect of angiotensin pathway modulators such as ACE inhibitors and ARBs, which dilate the efferent arteriole and reduce intraglomerular pressure and glomerular damage.[viii]

Sodium

Sodium intake is also an important factor in maintaining health in CKD because a decrease in urinary sodium excretion can lead to hypertension and edema. Borrelli et al., 2020, performed a meta-analysis on the relationship between sodium and CKD. CKD patients are sodium sensitive and high blood pressure (BP) is a recurrent finding with poor cardio-renal prognosis. A low sodium diet (LSD) or the heart healthy diet are suggested dietary modification by the American Heart Association for being cardiovascular protective. According to the World Health Organization (WHO), it is recommended to restrict sodium intake to less than 2.3 g/day, as this is one of the most cost-effective measures in improving the health of the public. [xxv] This study also reported the effect of salt restriction on proteinuria, a significant improvement of 0.4 g/day (95% C.I.: 0.2–0.6 g/day) associated with lower salt intake. [xxiv] These findings agreed with other evidence on LSD improving proteinuria and inhibiting RAAS. Although the effects of LSD on BP and proteinuria suggest an improvement of prognosis in CKD patients, few studies have evaluated the long-term effect of salt restriction on the cardio-renal outcomes [xxiv]. The aforementioned Modification of Diet in Renal Disease (MDRD) Study found no association between a single baseline 24-hour urinary sodium excretion with kidney failure and a composite outcome of kidney failure or all-cause mortality. [viii] Additionally, another study, O'Donnell et al., 2014, found that sodium intake of <3 grams forecasted a higher CV risk, following a lower incidence of disease in the middle ranges, with peaks in both the lower and upper ranges. [xvii] However, this study was methodologically flawed by multiple factors such as biased methods to assess individuals

salt intake, reverse causality such as getting sick and having lower sodium intake, and the relationship that lower sodium intake may result in lower protein intake. In the Borrelli et al., 2014 study, the harmful effects of sodium on blood pressure values are worsened in CKD patients. Damage to the heart, kidneys, and volume overload were observed. [ii] In non-dialysis CKD patients, a low sodium diet is beneficial for hypertension control, regardless of blood pressure levels. Additionally, it correlated enhancing the antiproteinuric effect of RAAS inhibition, decreasing proteinuria. Because of the common mismatch between intake and removal of sodium by dialysis, sodium restriction assumes a greater importance in ESKD .[x] Concluding that, reducing salt intake is crucial for earlier staged CKD patients. However, this remains insufficiently and or inadequately applied in clinical practices.[x]

Mediterranean Diet

In a newer approach, the Mediterranean diet is being analyzed for diet therapy in CKD patients. [xvi] The Mediterranean diet consists of: high intake of produce such as fruits and vegetables. Additionally, the diet consists of a well-balanced intake of foods such as, whole-grain bread and cereals, legumes, nuts, seeds, and olive oil. A moderate intake of dairy products, egg, seafood, poultry, and wine; and primarily using fish or chicken as protein. [v] Huo *et al.*,2014, explored the effects of a Mediterranean diet on glycemic control and cardiovascular risk factors, finding that adherence was associated with reduced levels of HbA1c (serum marker for diabetes), fasting glucose and insulin among patients with type 2 diabetes. [xi] It was also found to significantly reduce hemoglobin A1c and glucose in the general population without diabetes as well.

Concluding that the management of type 2 diabetes may improve with adherence to a Mediterranean diet and ultimately slow renal function decline. Furthermore, this study found that the Mediterranean diet led to a reduction in blood pressure and low-density lipoprotein and higher estimated glomerular filtration rate (eGFR) in people with CKD. [xi]

A cross-sectional observational study, Bowden et al., 2021, participants with non-dialysis dependent CKD stages 3 to 5 were recruited via convenience sampling and categorized by the eGFR NKF clinical guidelines.[iii] The authors observed no significant association between adherence to a Mediterranean lifestyle and CKD. However, this study is limited by the small sample size and had poor support in the use of different tools to measure adherence to the Mediterranean diet. Comparatively, another cross-sectional study with a larger population (N=2813), Heindel et al. 2020, found that patients with CKD stage 3 that better adhered to a Mediterranean diet had a higher eGFR. [ix]

In a prospective cohort study (Hu et al., 2020), 2,403 participants were followed on different diets to analyze the effects each diet would have on estimated glomerular filtration rate. The participants were age 21-74 with an eGFR) of 20–70 mL/min. The criteria used dietary data in the Chronic Renal Insufficiency Cohort (CRIC) study. These participants diets were analyzed with calculations from food frequency questionnaires, including: The Healthy Eating Index-2015 (HEI-2015), Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean diet (aMed), and Dietary Approaches to Stop Hypertension (DASH) diet. Participants were sorted as low and high adherent groups. Overall, aMED demonstrated the strongest results for lowest risk in CKD progression; aMed was associated with a 25% reduced risk of CKD progression.[x]

Overall, diet is effective, however, results are mixed due to different regimens. Diet can be a huge contributor to the management and care of CKD patients but most clinicians do not know how to use diet in clinical practice and need to be educated.

METHODS

Study design

An educational workshop on dietary therapies and guidelines for patients with CKD stages 1-3b will be developed by a registered dietician who works primarily with CKD patients. A current analysis on the effects of dietary interventions such as LSD, LPD, and the Mediterranean diet for CKD will be presented to the workshop participants. The goal is to educate health care providers and measure knowledge gained on the different types of diet therapy that are beneficial for patients with CKD. The aim is to prepare participants and provide patient education confidently in an engaged conversation about the benefits of diet modifications and chronic kidney disease. All participants must sign a consent form agreeing their participation and responses may be used for research and available to the public. This workshop will be presented at medical conferences and offered 1 CME credit.

Study population

The workshop will be given at medical conferences in the Boston metropolitan area (North Shore, South Shore, Framingham, and Providence) by a registered dietitian who primarily works with CKD patients. The participants who register for this conference must be active medical professionals with up-to-date licenses, such as primary care physicians, nephrologists, nurse practitioners (NPs), and physician assistants (PA-Cs). The expected effect of a new inquiry of research is typically small, in this case small to medium, for a workshop on learning dietary therapies targeted for kidney disease.

Therefore, based on Cohen's d, a small to medium effect size (d) of 0.3, an alpha (two tailed) of 0.5, and 80% power, we will need a minimum sample size (N) of 90.[xxv]

Intervention

The review will be presented in a 90-minute lecture. This will be directed towards mid- to high-level clinicians, such as, primary care physicians, nephrologists, PA-Cs, and NPs. However, it will be available to other healthcare providers, such as nurses, nutritionists, and other specialty physicians, who are interested in learning more about diet therapy for CKD patients.

The curriculum will take the format of a workshop accompanied by a Powerpoint presentation. The learning objectives (LO) (Appendix 1) will be presented at the beginning of the workshop and will go over important aspects of the workshop. The focus of these LOs will be about identifying different diet therapies available and proposed differences in clinical outcomes, recognizing their effectiveness, and providing patient-provider dialogue to educate patients within clinical practices. A majority of the lecture will focus on these LOs, including, being able to identify different diet therapies available such as the Mediterranean diet, low protein diet, and salt diet and their proposed differences in clinical outcomes. Other LOs will include recognizing their effectiveness and providing patient-provider dialogue to educate patients within clinical practices.

Study measures and data collection

To verify how effective this curriculum is, all those who attended will perform a pre-test and post-test to assess baseline knowledge and knowledge following the workshop. The pretest will consist of 15 multiple choice questions delivered via

Examsoft, however answers will not be given. Each attendee will be provided with a tablet upon entering the workshop. At the end of the workshop, the same questions will be asked. The goal is to achieve an overall increase in dietary therapy knowledge.

The initial and final test will act as the main analysis of the ability of the curriculum to meet the LOs. The pre-test will measure the health care providers baseline knowledge on chronic kidney disease and what nutrients and dietary restrictions play a role in preventing and delaying worsening CKD. As mentioned before, the pre-test will be given to all attendees prior to the start of the workshop via ExamSoft created by the workshops registered dietician on a tablet that grades the test taker automatically. After the presentation, a post-exam will be given with the same questions. The content of the pre and post exams will have the fundamental principles in the LOs and will include questions on nutritional factors and their effects on kidney function and disease development (Appendix 2). Additionally, the attendees will be given a paper survey on the tablet polling their occupational title, specialty, and how helpful the knowledge acquired during the session will change their current practice (Appendix 3). There will be a written portion for them to write anonymous comments up to 1000 characters. This survey will automatically be saved online prior to the end of the workshop.

A one year follow up email will be sent to all participants with a five-question mailed paper survey. The survey will consist of 5 questions rating the impact the workshop had on the health care workers day to day practice (Appendix 4).

Recruitment

A research coordinator will contact the medical education directors of local hospitals in the metropolitan area of Boston to assess interest and available participants. Once participating hospitals agree to participate, the workshop will be held in their respective local medical conferences. The intention is for this workshop to be made accessible to all healthcare professionals but emphasizing the importance of attendance for physician associates working in primary care or nephrology. The research coordinator and medical education directors will then coordinate information about time and place of the workshop and make this information available on the hospital's website. The website will include an online registration account; those who register will be emailed a downloadable and printable document with a brief outline of the workshop. Attendance will be recorded with a sign-up sheet located at the door of the conference room. This will allow for all attendees that work in health care to receive 1 CME credit. The incentive is to help promote access to updated information on nutrition and nephrology for further attendance incentive.

Data analysis

The mean of the pre and posttest will be calculated. The pretest mean will reflect the basic knowledge of healthcare workers in attendance prior to the workshop. The posttest mean will reflect the knowledge acquired after the workshop. There is no goal or aimed mean score for the pretest as it is only for judging the healthcare workers' foundational knowledge.

To compare the mean between the pre- and post-tests, a paired t test will be used. There will not be a minimum anticipated value for score improvement. If there is a significant difference, then the attendees' knowledge improved from the pre to post workshop.

Timeline and resources

For the curriculum to be presented at medical conferences held in local state hospitals to PA-Cs, physicians, nurse practitioners, and other providers, it must be approved by the medical education coordinator. A research coordinator will first find a registered dietician who specializes in CKD. Once credentials are verified, this person will create the workshop content and present the information in a powerpoint presentation. Afterwards, the next step is for the research coordinator to reach out to the medical education coordinator at local hospitals in the metropolitan area of boston. For this study, 1-2 hospitals per area will need to be found. Hospitals that will be contacted will be non-profit only with dense patient populations. The anticipation for approval and scheduling of the workshop will take 6-12 months to be completed. Once approved by the medical education coordinator, participating hospitals will be submitted in the fall of 2023 or spring 2024. We believe it will take one year to present to all participating hospitals. The limitation is 2-3 teaching hospitals per metropolitan area of boston. Averaging 1-2 workshops per month at one hospital. The anticipated completion of data collection will be in spring of 2025. The follow up 5 question survey will be anticipated in Spring of 2026.

Institutional Review Board

The curriculum will be submitted at the level of an exempt review to the Institutional Review Board for approval for educational research.

CONCLUSION

Discussion

The information on dietary therapy and nutritional elements in preventing CKD has been found beneficial for CKD. Current research that has been published focuses on nutritional components and the renal protective effects. Identifiable risk factors such as obesity, diabetes, and high blood pressure, have been the target of much of this research. Many of the dietary and lifestyle modifications in literature focus on multiple complex nutritional elements, including but not limited to low salt diet, low protein diet, and the Mediterranean diet. This information can be applied to all stages of CKD, but more importantly clinically in managing early stage CKD and preventing ESKD.

Limitations in the found evidence include biased methods to assess the intake of nutritional elements such as salt and protein intake, promoting lower intake to support findings during times of sickness with already concurrent lower oral intake. Other biased methods focus on adherence to specific diets such as the mediterranean diet, low protein diet, and low salt diet, promoting higher adherence without proper documentation. Additional limitations included small cohorts and lack of long term follow up on disease with dietary modifications.

The potential obstacles of this study would be first finding medical conferences that will agree to host the workshop. Another obstacle would be whether the workshop will have enough registering participants, as 1 CME may not be enough to generate

interest. Additionally, recruiting a registered dietician that is not only interested in but qualified to host the conference for a prolonged period of time might be difficult to find.

The one year follow up questionnaire will help analyze whether there is improved knowledge of dietary therapy with individual clinicals. As well as, whether this change in an individual clinicians management utilizing dietary therapy in CKD management actually changes the progression of the disease and or if it lowers the burden of cost.

Summary

Chronic kidney disease is the ninth leading cause of death in America. It accounts for close to 50,000 deaths annually. An estimated 37 million Americans have chronic kidney disease (CKD). The majority of patients assigned as having CKD are aged over 60 years are estimated at 37 million who are at risk for kidney failure or end-stage kidney disease (ESKD) requiring dialysis or kidney transplant.[i] The majority of research done on improving CKD or ESRD survival has focused on either pharmaceutical therapy, dialysis, or transplant surgery. Because of certain genetic markers, comorbidities, and more identifiable risk factors and later clinical symptoms, people with ESKD are easier to identify and recruit for research studies than those who are predialysis and non symptomatic. ESRD due to its irreversibility and clinically aggressive nature, and worse prognosis, has been mainly focused on dialysis research and transplant care. In the U.S alone 786,000 people are living with ESKD, with 71% on dialysis and 29% with a kidney transplant.

Adjusted mortality varies depending on certain factors with CKD patients such as, being more than twice as high among Medicare beneficiaries ages 66 years or older with

CKD, decreased by nearly 15% or 20% in patients receiving hemodialysis and peritoneal dialysis, respectively, or being significantly lower in patients with a kidney transplant vs those on dialysis. Given the varying prognosis and high prevalence and mortality rates, there is a need for increased measures in delaying and regressing the development of CKD.

Salt, potassium, and protein have been the nutritional elements most studied for their effects on chronic kidney disease. Additionally, the Mediterranean diet has been studied as well for its effect on CKD. The aforementioned nutritional elements, diets, and lifestyle factors that have been proposed to be effective in reducing CKD development, ameliorate strong risk factors such as obesity, high blood pressure, and uncontrolled sugar levels, and directly improve early-stage kidney disease 1-3b and mortality. Overall, dietary therapy can delay the progression of patients with CKD and prevent CKD in non CKD patients, increasing overall survival in the general population and decreasing the need for dialysis or transplant surgery.

Clinical and/or public health significance

As one of the top 10 leading causes of death with high prevalence, mortality, coexisting complications, and expensive long-term care, CKD is in need of encompassing dietary therapy to prolong survival. However, due to the complex nutritional elements incorporated with managing this disease, formal training in nutrition and adequate preparation for providers is limited. Nutrition education is an area health care providers need to make improvements in regard to their medical training, as not all clinicians are training specifically to care for CKD/ESRD patients.

An education workshop providing the most updated information on different dietary therapies and nutritional elements and their effect on CKD development, highlighting its ability to slow down CKD progression and potentially prevent ESRD would be helpful in creating awareness in this area of research. The workshop will equip PAs and other healthcare professionals with the knowledge of recent advances in the area of CKD and nutrition/diet. It will work in conjunction with spreading awareness to the medical community. Aiding healthcare workers better tools to provide patient care with up-to-date information. Attendees of this workshop will be able to provide patients in their practice with nutritional and dietary lifestyles to minimize the progression of CKD.

APPENDIX

Appendix 1: Learning objectives

At the end of the workshop, the learner will be able to:
1. Identify the different diet therapies available and proposed differences in clinical outcomes with patients of CKD stages 1-3b.
2. Recognize the effectiveness in dietary therapy for patients in CKD stages 1-3b and the poorer prognostic outcome and advancement to ESRD without
3. Analyze the roles sodium, protein, and potassium have in kidney disease and how each can affect the eGFR
4. Apply the most recent data on dietary modifications and CKD to their clinical work
5. Create a patient-provider dialogue to educate patients about dietary recommendations pertaining to CKD and how it can prevent and decel the disease

Appendix 2: Question Topics

1. Different stages of Chronic Kidney disease a) 0-3, b) 1-4, c)0-5, and d) 1-5
2. What eGFR level is considered ESRD a) 60 eGFR, b) 45 eGFR, c) 30 eGFR, d) less than 10 eGFR
3. What biomarkers are used to diagnose CKD a) proteinuria, b) eGFR, c) urinary osmolarity, d) A and B
4. Overall prognosis of CKD and ESRD
5. Protein recommendation per day for patients with CKD stages 3-5 a) 1-1.5 g/day, b) 0.75-1 g/day, c) 0.25-0.5 g/day, d) 0.55-0.65 g/day
6. Protein recommendations per day for post kidney transplant patients a) 0.5 g/day, b) 0.8 g day, c) 1g/day, d) 2g/day
7. Sodium recommendations per day to lower risk of cardio-renal diseases

a) less than 2.3 g/day, b) more than 5 g/day, c) less than 0.5 g/kg/day
8. Effects of blood sugar on development of CKD a) no relationship, b) higher glucose levels are beneficial, c) lower sugar levels are beneficial
9. Effects of high blood pressure on development of CKD a) BP and kidney functions are independent, b) high blood pressure improves kidney functions, c) lower blood pressure improves kidney function
10. Overall effects of low vs high salt levels in CKD patients a) HSD improves kidney functions, b) LSD worsens kidney function, c) LSD improves kidney functions, d) alternating between HSD and LSD is best for CKD
11. Overall effects of low vs high protein levels in CKD patients 12. HPD improves kidney functions, b) LPD worsens kidney function, c) LPD improves kidney functions, d) alternating between HpD and LPD is best for CKD 13.
14. Effectiveness of DASH diet for reducing risk of progressive CKD a) only effective for heart disease patients with coexisting CKD, b) not effective at all for any CKD patients, c) effective
15. Effectiveness of Mediterranean diet for reducing risk of progressive CKD a) not effective, b) effective, c) effective only sometimes

Appendix 3. Survey

● Title (MD, PA-C, NP, RN, nutritionist, registered dietician, or other) ● Specialty (Primary Care, Nephrology, or other) ● On a scale of 1-5 (1 unhelpful and 5 most helpful): How helpful was it learning about dietary therapies and will this be used now in practice for treating CKD patients? ● Additional comments here (1000 characters max)

Appendix 5: 5 question survey

Question	1 (Not very likely)	2 (Not likely)	3 (Neutral)	4 (Likely)	5 (Very Likely)
How effective was the workshop in informing up to date knowledge?					
How often do you present the information you learn with patients day to day?					
Has the workshop changed your style of providing care in your current practice?					
Would you attend another workshop in the future?					
Do you feel your patient's care has improved over the year with this information?					

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