January 2020

Impact Of Dietary Patterns On Health Outcomes In African American Maintenance Hemodialysis Patients

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IMPACT OF DIETARY PATTERNS ON HEALTH OUTCOMES IN AFRICAN AMERICAN MAINTENANCE HEMODIALYSIS PATIENTS

by

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DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

2020

MAJOR: NUTRITION AND FOOD SCIENCE

Approved By:

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Advisor Date

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DEDICATION

This work is dedicated to

My husband – Steve Tallman

My children – Emily and Mark Tallman

My parents – Jeffrey and Marilyn Krok

and

My PhD advisor Dr. Pramod Khosla

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Dr. Pramod Khosla, for his guidance, support, and invaluable feedback throughout my research. Additionally, a sincere thanks to the other members of my dissertation committee, Dr. Smiti Gupta, Dr. Paul Burghardt, and Dr. James Sondheimer. Thank you to Dr. Deepinder Kaur for being an amazing mentor, and to previous and current lab members, Bayan Tashkandi, Tanjina Rahman, Skylar Mast, Ushaasri Gullapalli, and Eno Latifi.

I would also like to thank faculty at Taylor's University, Malaysia, Professor Tilakavati Karupaia and Dr. Karuthan Chinna, and at Universiti Putra Malaysia, Dr. Zulfitri 'Azuan Mat Daud, as well as colleagues at Universiti Kebangsaan Malaysia, Sharmela Sahathevan, Dr. Ban Hock Khor, and Ayesha Sulaheen. I had the privilege to both receive training from our Malaysian colleagues for Palm Tocotrienols in Chronic Hemodialysis (PATCH), and to present with them at the Advance Course in Renal Nutrition and Metabolism and Workshop on Nutritional Screening & Assessment, Lucknow, India.

Additional thanks to the nephrologists, nurses, and dietitians involved in the PATCH USA study, Dr. Lalathaksha Kumbar, Nicole Smiley, RN, and Emily Wesley, RD from Henry Ford Hospital; Dr, Boniface Tubie and Marina Sheyman, RD from Great Lakes Dialysis; Matt Rymond, RD from DaVita; Dr. Saroj Bhat, Debbie Sweetapple, RD, and Linda Savona, RD from Henry Ford Hospital Fairlane Dialysis; Melissa Hale, RD from DaVita Redford; and Krista Gregory from DaVita Highland Park.

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LIST OF ABBREVIATIONS AND ACRONYMS

AA – African American

BMI – Body Mass Index

CMS – Centers for Medicare and Medicaid Services

CKD – Chronic Kidney Disease

CKD-MBD – Chronic Kidney Disease Mineral and Bone Disorder

CVD – Cardiovascular Disease

DEI – Dietary Energy Intake

DM – Diabetes Mellitus

ESRD – End Stage Renal Disease

FGF23 – Fibroblast Growth Factor 23

GFR – Glomerular Filtration Rate

JHS – Jackson Heart Study

HD – Hemodialysis

HDL-C – High-Density Lipoprotein Cholesterol

HGS – Hand Grip Strength

HTN – Hypertension

IDWG – Interdialytic Weight Gain

KDIGO – Kidney Disease: Improving Global Outcomes

KDOQI – Kidney Disease Outcomes Quality Initiative

KDQOL – Kidney Disease Quality of Life

LDL-C – Low-Density Lipoprotein Cholesterol

MAC – Mid Arm Circumference

MAMC – Mid Arm Muscle Circumference

MHD – Maintenance Hemodialysis

MUFA – Monounsaturated Fatty Acids

NKF – National Kidney Foundation

NHANES – National Health and Nutrition Examination Survey

PATCH – Palm Tocotrienols in Chronic Hemodialysis

PROM – Patient Reported Outcome Measures

PTH – Parathyroid Hormone

RDA – Recommended Dietary Allowance

RRT – Renal Replacement Therapy

SHPT – Secondary Hyperparathyroidism

PEW – Protein Energy Wasting

PUFA – Polyunsaturated Fatty Acids

QOL – Quality of Life

TAG – Triglycerides

TC – Total Cholesterol

TSF – Triceps Skin Fold

UFR – Ultrafiltration Rate

USDA – United States Department of Agriculture

CHAPTER 1: INTRODUCTION

Background and Clinical Significance

Kidney Structure

Each kidney, about the size of a fist and located on either side of the spine, is made up of approximately one million functioning units called nephrons. Each nephron includes a glomerulus, surrounded by a single layer of epithelium called the Bowman's capsule, and a long tubule which consists of a proximal portion and a distal portion connected by a loop of Henle. The tubule joins a collecting duct which joins larger ducts, eventually draining into the renal pelvis (Figure 1).

Blood enters the glomerulus via the afferent arteriole, and filtered blood (ultrafiltrate) is carried away from the glomerulus via the efferent arteriole. Both the afferent and efferent arterioles have a muscular layer which allows them to dilate or constrict (Figure 1) [1-3].

Kidney Function

The kidneys are best known for their role in excreting metabolic waste products through urine production; however, these organs are responsible for other essential tasks, such as regulating blood volume, maintaining acid-base balance, and assuring bone integrity and blood pressure control. The nephrons of the kidney regulate blood composition within a narrow physiologic range via three main processes: filtration, reabsorption, and secretion.

Glomeruli in the nephrons are responsible for generating ultrafiltrate of the plasma. Filtration is based on size and charge, where small solutes (e.g., glucose, urea, insulin, and ions – sodium, potassium, bicarbonate, and chloride) are able to readily cross the filtration barrier, larger substances (e.g., cells and immunoglobulins) are generally excluded, and negatively charged molecules such as large plasma proteins (e.g., albumin) are restricted.

As the ultrafiltrate flows from the Bowman’s capsule of the glomerulus through the tubules, its composition changes as solutes and water are reabsorbed out of the ultrafiltrate (tubular

reabsorption) and substances such as hydrogen ions, creatinine, and xenobiotics are removed from the blood through the peritubular capillary network into the collecting duct (tubular secretion) [1, 4].

Any substance that has not been reabsorbed during glomerular filtration or tubular reabsorption is excreted in the urine, which is composed of 95% water and 5% various solutes, of which 60% is nitrogenous waste (urea, uric acid, creatinine, and ammonia) and 40% is inorganic salts (sodium chloride, calcium phosphate, calcium sulfate, sodium, potassium, and magnesium).

The kidneys are also responsible for producing and releasing three important hormones: erythropoietin, calcitriol (1,25-dihydroxycholecalciferol or 1,25(OH)2 D), and renin. Erythropoietin is a peptide hormone which stimulates red blood cell production in the bone marrow. Calcitriol is the biologically active form of vitamin D; the proximal tubule of the kidney provides the enzyme, 1-alpha hydroxylase, responsible for the final hydroxylation reaction in converting calcifediol to calcitriol. Renin helps regulate blood pressure and fluid balance; this enzyme is released by the granular cells in the juxtaglomerular apparatus of the kidneys in response to a fall in arterial blood pressure or sodium levels. Additionally, the kidneys have metabolic roles, such as metabolizing certain drugs and endogenous substances such as insulin, as well as some capacity to conduct gluconeogenesis [5-7].

Epidemiology of Chronic Kidney Disease (CKD)

CKD cause can be classified by the presence of underlying systemic disease, such as diabetes mellitus (DM), autoimmune disorders, and genetic disorders, or by diagnosis of an anatomic abnormality of the kidney (i.e., glomerular, tubulointerstitial, vascular, or congenital).

Clinical, sociodemographic, genetic, and epigenetic risk factors may contribute to CKD risk. The two primary clinical risk factors for kidney damage in the United States (U.S.) are DM

and hypertension (HTN). Other clinical risk factors include nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDs), obesity, kidney stones, and smoking. Since many patients fail to receive nephrology care prior to diagnosis, the actual cause of their CKD may be attributed erroneously to DM or HTN, leading to over reporting of these two conditions [8].

Among the sociodemographic factors that contribute to increased CKD risk are nonwhite race, progressive age > 60, low education, and low income.

Genetic risk factors include apolipoprotein L1 (APOL1) risk alleles, polycystic kidney disease, sickle cell trait and disease, and congenital anomalies such as glomerulocystic kidney disease (GCKD). Several single gene disorders, such as GCKD, are known as "monogenic diseases" or mutations of a single gene and are fully penetrant and thus evident from birth or early childhood. Genetic disorders which affect multiple genes are polygenic, such as autosomal dominant polycystic kidney disease, and typically present later in life [9, 10].

Epigenetics may also play a role in CKD development and explain susceptibility to comorbidities such as obesity or DM. Environmental and lifestyle factors, such as diet, nutrition, behavior, stress, and physical activity, can result in inflammation, oxidative stress, and uremia, which induce epigenetic changes leading to renal fibrosis and CKD development [11, 12].

Pathophysiology and Risk Factors for CKD

CKD is a condition generally characterized by a slow and progressive loss of kidney function over time as a result of several heterogeneous disease pathways that irreversibly alter the function and structure of the kidney. Renal fibrosis, which is the unsuccessful wound healing of kidney tissue after chronic, sustained injury, is the final common pathological manifestation resulting from a variety chronic kidney diseases. This fibrotic tissue in the kidneys is a buildup of scar within the parenchyma and is characterized by glomerulosclerosis, tubular atrophy, and

interstitial fibrosis. Risk factors for progressive glomerulosclerosis, or scarring or hardening of the glomeruli, include hyperglycemia, HTN, dyslipidemia, and smoking [13, 14].

Clinical Presentation of CKD

The kidney possesses a huge physiologic reserve which can explain why most CKD patients are asymptomatic until more than 75% of kidney function is lost. As CKD progresses, kidney function becomes less effective, leading to the accumulation of uremic retention solutes and uremic toxins that can exert adverse biological effects in the body. These toxins are believed to contribute to inflammation, immune dysfunction, cardiovascular disease (CVD), gut dysbiosis, and further CKD progression. Uremic retention solutes can be subdivided into three groups based on their solubility, binding capacity, and molecular size: (1) small water soluble compounds (i.e., urea, polyamines, and oxalates), (2) small protein-bound or lipid soluble compounds (homocysteine and indoles), and (3) larger (over 500 Da) middle-molecules (β2 microglobulin, parathyroid hormone, and advanced glycosylation end [AGE] products).

Diagnosis of CKD

Estimated glomerular filtration rate (GFR), a measure of kidney function, and albuminuria, a marker of kidney damage, are the two main tests used to detect and stage chronic kidney disease. GFR, which equals the total amount of fluid filtered through all of the functioning nephrons per unit of time, is calculated from serum creatinine or cystatin C levels using an estimating equation (e.g., the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] [15] and Modification of Diet in Renal Disease Study [MDRD] [16] equations) in combination with age, race, and gender, whereas albuminuria is directly measured from urine as albumin to creatinine ratio. Current Kidney Disease Improving Global Outcomes (KDIGO) guidelines define CKD, regardless of underlying cause, as decreased kidney function evidenced by GFR of < 60 mL/min per 1.73 m^2,

or albumin to creatinine ratio > 30 mg/g, or both, for at least 3 months (Figure 2) [17]. The rate of progression through the stages can vary based upon several factors, such as underlying disease, comorbidities, socioeconomic status, genetics, and ethnicity [18].

Because both the MDRD study and CKD-EPI equations are based on serum creatinine, these equations are not recommended for use in persons with extremes in muscle mass and dietary protein intake. Additional confirmatory tests can be used if routine test results are uncertain. In the case of abnormal muscle mass or extreme protein intake, serum cystatin C with or without creatinine can be used to assess kidney function since serum concentrations of cystatin C are less influenced by diet and muscle mass than creatinine. Also, abnormal muscle mass, extreme protein intake, urinary tract infection, heavy exercise, and menstruation may affect the accuracy of urine albumin to creatinine ratio, in which case albumin excretion rate in a timed urine collection should be used for assessment [17, 19].

Current United States (U.S.) Preventive Services Task Force guidelines do not recommend screening for kidney disease in asymptomatic individuals in the general population [20]. However, per KDIGO guidelines, regular testing is recommended for those in high-risk populations, such as patients with HTN, DM, CVD, and family history of kidney failure [17].

Treatment of CKD

Once a diagnosis of CKD has been established, both dietary and pharmacotherapy can be initiated in an effort to slow the progression of further renal damage.

Medications such as angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors work by decreasing the tone or dilating the efferent arteriole, thus reducing the pressure in the glomerulus. Both drugs are more effective than other antihypertensive drugs in slowing the rate progression of proteinuric CKD [21].

Low protein diets (LPD) with or without keto acid analogs have been shown to potentially delay further kidney damage. Provided there is adequate caloric intake, either a LPD providing 0.55 to 0.60 g of dietary protein/kg ideal body weight/day, or a very LPD providing 0.28 to 0.43 g of dietary protein/kg ideal body weight/day with additional keto acid analogs to meet protein requirements (0.55 to 0.60 g/kg body weight/day) is recommended for adults with CKD 3-5 who are metabolically stable [22-24]. For adults with CKD stages 1-4, diets high in fresh fruits and vegetables are suggested to improve lipids, body weight, blood pressure, and net acid production. Additionally, adults with CKD 1-5 (non-dialysis), with or without dyslipidemia, following a Mediterranean Diet is recommended to potentially improve lipid profiles [25-27].

Interventions are not always effective at delaying the progression of CKD. Consequently, people with CKD are five to ten times more likely to die prematurely than they are to progress to ESRD, primarily attributable to cardiovascular disease [28]. In fact, CVD risk is increased at a GFR of about 75 mL/min and increases continuously as renal function declines [29]. Kidney diseases were the 9th leading cause of death in the U.S. in 2017 and the 12th most common cause globally [30, 31]. Furthermore, CKD mortality has increased by 31.7% over the last 10 years, becoming one of the fastest rising causes of death worldwide [32].

End Stage Renal Disease (ESRD)

Unfortunately, many diagnoses for CKD are made only following chance findings from screening tests or after symptoms become severe. A patient with a GFR of less than 15 mL/min/1.73m^2 is in the final stage of CKD, ESRD Stage 5, at which point renal replacement therapy (RRT) is considered. Patients requiring RRT must weigh their options to receive either dialysis (ESRD Stage 5D) or a kidney transplantation (ESRD Stage 5T) for survival [8].

The 2012 KDIGO guidelines suggest that dialysis be initiated when one or more symptoms or signs attributable to kidney failure are present. Rationale for initiation of dialysis includes

serositis, acid-base or electrolyte abnormalities, pruritus, inability to control volume status or blood pressure, progressive deterioration in nutritional status that cannot be managed by dietary interventions, and cognitive impairment. These signs and symptoms often occur in the GFR range between 5 and 10 mL/min/1.73 m^2 [17].

After determining that RRT is medically indicated, the patient receives evaluation and counseling to discuss receiving either maintenance hemodialysis (MHD) (in-center or at home), peritoneal dialysis (continuous or intermittent modalities), or renal transplantation (living or deceased donor). The majority of patients with ESRD are treated with intermittent (2-3 days per week) HD to remove fluid volume and kidney wastes.

Whereas dialysis replaces only the non-endocrine functions of the kidney, organ transplantation replaces both the endocrine and non-endocrine functions. Kidney transplantation is the most cost effective modality of RRT and provides the best prognosis for survival; however, demand greatly outweighs the supply of donor kidneys. In 2014, the waiting list for a donor kidney was 2.8 times larger than the availability of donated organs [33].

United States Renal Data System (USRDS)

Funded directly by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the United States Renal Data System (USRDS) is a national data system that collects, analyzes, and distributes information about CKD and ESRD in the U.S. Most of the USRDS analyses are based from Centers for Medicare & Medicaid Services (CMS) enrollment and claims data since ESRD is a covered service under Medicare [34].

Economic Burden of ESRD

There are currently more than 468,000 Americans on dialysis [35]. Total Medicare costs (excluding prescription drugs) for patients with ESRD accounted for 7% of Medicare fee for-service (FFS) spending, while making up only about 1% of total program enrollment [36].

Traditional and Non-Traditional Cardiovascular Risk Factors

For those patients who do progress to ESRD, mortality due to CVD is reported as 20 times higher than in the general population. Per the 2018 USRDS, CVD mortality due to arrhythmia and cardiac arrest comprised 40% of known causes of death among dialysis patients [37]. Most MHD patients experience CVD complications due to both traditional [38, 39] and non-traditional risk factors. Traditional risk factors include age, male gender, HTN, dyslipidemia, and smoking. Non-traditional risk factors, or uremia related factors, include ventricular hypertrophy, chronic volume overload, anemia, oxidative stress and inflammation, chronic kidney disease mineral bone disorder (CKD-MBD), and protein energy wasting (PEW) [40, 41].

Oxidative Stress and Inflammation

ESRD patients on MHD suffer from excessive oxidative stress, which has been associated with an increased risk for CVD and all-cause mortality. The HD procedure itself results in a significant loss of antioxidants, while the bioincompatibility of dialyzers and dialysate trigger the production of free radicals [42].

Biochemical indicators of systemic persistent inflammation include the most widely used inflammatory marker, C-reactive protein (CRP), and cytokines, such as interleukins 6 (IL-6) and 18 (IL-18), and the chemokine monocyte chemoattractant protein-1 (MCP-1) (Figure 3). As a result from both increased tissue production of inflammatory mediators and their retention due to inadequate renal removal, MHD patients typically have higher levels of inflammatory markers. When compared to the general population, serum concentrations of CRP and IL-18 are up to 2- to

3-fold higher for CKD patients as compared with controls [43, 44]. In addition to inflammation induced by uremic toxins, obesity, physical inactivity, and smoking also contribute to increased inflammation [45]. Higher levels of CRP, an acute phase protein produced by hepatocytes, have been positively associated with mortality in dialysis patients [46, 47].

Higher levels of IL-18, a cytokine primarily produced by Kupffer cells (liver-resident macrophages) [48], are associated with an increased incidence rate of major adverse cardiovascular events in HD patients [49]. This proinflammatory cytokine is involved in the process of atherosclerotic plaque formation [50] and is positively correlated with hospitalization, vascular injury, and all-cause mortality in HD patients [51].

Elevated levels of IL-6 are commonly observed in HD patients not only due to increased generation from chronic inflammation, comorbidities, uremic factors, and reduced cytokine clearance [52], but also due to the dialysis procedure itself [53, 54]. IL-6 has been shown to initiate endothelial injury thus contributing to increased incidence of CVD in CKD patients [55]. As a major regulator of acute phase proteins including CRP, albumin, and fibrinogen, IL-6 has been reported to be a better predictor of CVD complications and mortality than CRP and IL-18 [56-58].

MCP-1 is a chemokine produced by macrophages, endothelial cells, and vascular smooth muscle cells. This inflammatory cytokine mediates recruitment of monocytes into the subendothelial space at sites of inflammation. The monocytes differentiate into macrophages, ingesting lipids to form foam cells, initiating atherosclerosis [59, 60]. MCP-1 is expressed at high levels in macrophage-rich areas of atherosclerotic plaques, further contributing to the progression of atherosclerotic disease [61]. In patients with acute coronary syndrome, an increase of MCP-1 levels are correlated with CVD outcomes independent of traditional CVD risk factors [61] and

with atherosclerotic events and death in persons with CKD [62] as well as associated with an increased risk for restenosis of arteriovenous fistulas following postangioplasty [63].

Dyslipidemia

Both diet, genetics, lifestyle, and comorbidities can affect lipoprotein composition and functions. These lipoproteins are an essential group of soluble proteins that combine with and transport fat or other lipids in the blood plasma. Classified on the basis of density and electrophoretic mobility, there are seven classes of lipoproteins based on size, lipid composition, and apolipoproteins: chylomicron, chylomicron remnants, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and Lp(a).

Abnormalities in lipoprotein metabolism, associated with a decline in GFR, are one of the main factors in the pathogenesis of atherosclerosis and CVD in the HD population [64]. As opposed to hyperlipidemia, it is a dyslipidemic abnormal serum lipid profile that is commonly observed in ESRD HD patients. The pathogenesis of dyslipidemia is complex and caused by dysregulation in key enzyme activity and metabolic pathways. Dyslipidemia characteristic of HD patients includes (1) low HDL cholesterol (HDL-C), which is dysfunctional in its anti-oxidative and anti-inflammatory roles [65], and a decrease in ApoA-I and ApoA-II levels (two major apolipoproteins associated with HDL), (2) elevated triglycerides (TAG), (3) relatively normal total cholesterol (TC), and (4) relatively normal LDL cholesterol (LDL-C), but with an increase in IDL and small, dense LDL-C and a decrease in larger LDL particles. These LDL and HDL particles are often modified by the oxidative process. Additional modifications include decreased lecithin-cholesterol acyltransferase (LCAT), increased cholesteryl ester transfer protein (CETP) activity, and downregulation of lipoprotein lipase and the LDL receptor [66, 67].

Small, dense LDL are thought to be more atherogenic than larger LDL particles. Beyond lipid levels or lipoprotein size, it is believed that lipoprotein particle "cargo" can affect atherosclerosis development and progression since lipoprotein particles transport many bioactive lipids, proteins, hormones, and microRNAs. In a 2015 study which compared the molecular lipidomic profile of LDL between stage 4/5 CKD subjects and non-CKD controls, Reis et. al. found that while total lipid and cholesterol content was unchanged, lipid subclasses were altered; LDL particle composition of CKD patients had significantly increased TAG and *N*-acyltaurines and significantly decreased phosphatidylcholines, plasmenyl ethanolamines, sulfatides, ceramides, and cholesterol sulfate [68]. Hu et. al. also found significantly lower levels of sulfatides for HD patients with CVD compared to those without CVD, and also found no differences in the levels of TC, HDL-C, and TAG between groups [69]. Many of these lipid species are known to have beneficial properties, such as the role of plasmalogens as antioxidant agents [70] and the anticoagulant effects of serum sulfatides [71].

Worse survival rates in ESRD patients have been associated with U-shaped (in Hispanic MHD patients) [72] or J-shaped (31.8% AA MHD patients) serum HDL-C levels. In the latter analysis including more than 33,000 HD patients, an increased risk for total and CVD mortality was reported in patients with HDL-C concentrations < 30 mg/dl and > 60 mg/dl [73].

Using more sophistical techniques, such as density gradient ultracentrifugation, HDL can be further subdivided into two major subfractions: HDL_2-C (larger, more buoyant) and HDL_3-C (smaller, denser), although results have been conflicting about which subpopulations are more protective [74]. The Jackson Heart Study (JHS) is one of the largest AA community-based, longitudinal cohort studies evaluating risk factors for CVD development and progression. Among 4,114 non-CKD participants in the JHS study, HDL_3-C rather than HDL_2-C, was found to be the

main inverse predictor of HDL-associated risk [75], while in another study of Japanese-Americans, it was HDL_2-C that was more atheroprotective [76]. HDL_2-C particles are involved in removing cholesterol from foam cells [77] and in preventing LDL oxidation [78].

There has been conflicting data regarding the predominant subclass of HDL-C in CKD patients, which may be due to confounding factors such as ethnicity and lifestyle. Several studies have reported a shift toward the HDL_3-C subclass in ESRD patients on HD [65], whereas others have reported a decrease in HDL_3-C with increasing CKD severity [79]. Nascent HDL particles are transformed into discoid HDL_3 and then should mature into spherical HDL_2 enriched with cholesterol, but because LCAT activity and level is impaired in HD patients, there is more HDL_3 and less HDL_2 [80]. However, LCAT is also essential for HDL maturation of lipid poor nascent HDL to lipid rich spherical HDL_3 [81].

Recently, the Quantimetrix Lipoprint Lipoprotein Subfractions Testing System was developed to measure LDL and HDL particle size via gel electrophoresis [82]. Few studies have reported on results using this system for the CKD population. In a Polish cohort of 115 CKD patients in CKD stages 2-5D and 25 healthy controls, Rysz-Górzyńska, et. al. reported that large HDL subfractions were more prevalent in CKD patients versus small HDL subfractions in healthy subjects [83]. Subfractions obtained by the Lipoprint system have not been correlated to the subclasses reported in the literature; therefore, it is difficult to compare results from studies using other separation techniques. The Lipoprint system has been compared to a previously validated technique, polyacrylamide gradient gel electrophoresis (PGGE), and good agreement was found to determine LDL size distribution, but not absolute LDL size [84].

Serum non–high-density lipoprotein cholesterol (non–HDL-C), or the difference between TC and HDL-C, which accounts for the proatherogenic cholesterol content of lipoprotein particles

(LDL, Lp(a), and TG lipoproteins IDL, VLDL, and CM) has been described as superior to LDL-C in CVD risk estimation for the general population [85]. However, a paradoxical association was found among 51,185 U.S. MHD patients (31.9% AA) with reduced levels of non–HDL-C with increased CV mortality and poor overall survival. Non-HDL-C levels < 100 mg/dL were associated with significantly higher mortality risk with the highest all-cause and cardiovascular mortality being observed in patients with a non-HDL/HDL-C ratio of < 2.5 [86].

While statins have proven effective in improving CV outcomes in the general population, randomized trials, such as the 4D study (Die Deutsche Diabetes Dialyse Studie) [87] and AURORA study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) [88], have demonstrated that there is no benefit from statin therapy in reducing CV events in the ESRD population.

The most recent guideline for management of dyslipidemia in CKD was published in 2003 by Kidney Disease Outcomes Quality Initiative (KDOQI) and is based on the Adult Treatment Panel III Guidelines from the National Cholesterol Education Program [89], which includes monitoring LDL-C, HDL-C, TAG, TC levels (using the Friedewald formula) [90]. However, the KDIGO work group formed to evaluate the KDOQI guidelines developed a new guideline. This KDIGO group does not recommend using LDL-C as a treatment target given that initiation of statins is no longer recommended for HD patients; however, discontinuation of statin therapy is not recommended for patients already receiving these agents at dialysis initiation [91].

Based on the 2003 KDOQI guidelines, CKD patients with dyslipidemia should initiate therapeutic life-style changes (TLC) if: (1) TAG > 500 mg/dL, (2) LDL-C > 100 mg/dL, and (3) TAG ≥ 200 mg/dL and non-HDL-C ≥ 130 mg/dL. TLC are shown in Figure 4 and include limiting

dietary cholesterol to < 200 mg per day, limiting total fat to 25-35% of total calories, increasing fiber to 20-30 grams per day, and improving glycemic control [89].

However, it has been demonstrated that there is little benefit in implementing additional dietary restrictions aimed at lowering lipids superimposed on the standard renal diet. In a small interventional study published in 2001 which evaluated the effect of trying to comply with established lipid-lowering recommendations superimposed on the normally prescribed dialysis diet over 14 weeks (n = 41), it was found that HD subjects decreased saturated fat intakes by 18% and cholesterol intakes by 16%, but energy intakes also decreased by almost 10%. Additionally, patients had problems in maintaining compliance with the modified dialysis diets [92].

Protein Energy Wasting (PEW)

PEW, a term proposed by the International Society of Renal Nutrition and Metabolism (ISRNM), is associated with higher morbidity and mortality in the HD population. ISRNM has defined PEW syndrome as “the state of decreased body stores of protein and energy fuels.” Loss of muscle mass has been suggested as the most valid criterion for PEW diagnosis [93], with CKD induced muscle protein degradation as the main determinant of muscle protein wasting [94]. A diagnosis of PEW can be made if three of the four criteria are met as outlined in Table 2: namely, reduced visceral protein stores, reduced BMI or weight loss, reduced muscle mass, and unintentional low DPI or DEI for at least two months. The pathophysiology of PEW is complex and attributed to many factors, including malnutrition, aging, metabolic acidosis, uremic toxins, and inflammation [95]. Impairment of lipid metabolism also contributes to weight loss and cachexia due to the role of lipids in the production and storage of energy [96]. Measures of muscle mass are inversely related to systemic inflammatory markers, suggesting that cytokines play an important role in the development of PEW and muscle catabolism [97]. Chronic inflammation is

strongly associated with both CVD and PEW in patients on HD [98, 99]. The nexus of protein energy wasting, inflammation, and atherosclerosis is linked to poor quality of life and increased morbidity and mortality in ESRD [100].

Sarcopenia

Whereas PEW is characterized by a loss of muscle mass, sarcopenia is defined as (1) low muscle strength, (2) low muscle quantity or quality, and (3) low physical performance. Patients with one of these criterion have probable sarcopenia; two criteria indicate a sarcopenia diagnosis, and in those with all three criteria, sarcopenia is considered severe [101]. The European Working Group on Sarcopenia in Older People (EWGSOP) published this definition of sarcopenia in 2010 and met again in 2018 to provide clear cut-off points for these criteria (Table 3) [102]. Muscle strength, which declines more rapidly than loss of muscle, can be measured using a hand grip dynamometer. This loss of strength has been shown to be profound among healthy AA, who lose about 28% more muscle strength than whites [103]. Muscle quantity or quality should ideally be measured using DEXA or BIA, whereas anthropometry, while not as good a measure of muscle mass, can be used for both screening of sarcopenia and observational study purposes [104].

Whereas "primary" sarcopenia is considered to be age-related, "secondary" sarcopenia occurs as a result of systemic diseases, such as CKD, with a reported prevalence of 14% to 63% among ESRD patients [105]. Further contributing to the development of sarcopenia is physical inactivity and poor nutrition [102].

ESRD Disparities in African Americans

In the U.S., African Americans (AA) suffer a disproportionate burden of ESRD, accounting for 35% of all dialysis patients, and are 3.7 times more likely to progress to ESRD than whites [8, 106]. Racial disparity of excessive CKD burden in AA results from not only socioeconomic, lifestyle, and clinical factors, but also from genetic factors. Increased CKD risk in AA is partially

attributed to higher rates of HTN, DM, and CVD, which may be related to African ancestry, such as sickle cell trait and variants in the APOL1 gene [107-111]. In fact, sickle cell trait and the presence of two APOL1 risk alleles may double the risk of CKD [9, 110, 112].

Approximately 13% of the U.S. AA population carries the APOL1 high-risk genotype. It is theorized that this gene variant developed as an evolutionary mechanism of defense against the African Trypanosoma parasites, which are transmitted by the tsetse fly and are responsible for African sleeping sickness or trypanosomiasis. For APOL1 gene variants, the odds of having FSGS are 17 times greater and for HIV-associated nephropathy, 29 times greater. For AA carrying two APOL1 risk alleles, the risk for glomerular disease and FSGS occurs earlier and progresses to ESRD more rapidly [113]. Approximately 20% of AA with an APOL1 risk genotype develop ESRD; however, much is still unknown about the pathogenesis and phenotypic response to environment and comorbidities. Clinical interventions for those who carry the APOL1 risk genotype are currently not available; therefore, APOL1 testing is controversial [114]. However, testing for this gene variant may correctly identify CKD etiology, as many AA have ESRD caused by G1 and G2 renal-risk variants in the APOL1 gene, yet the cause of their renal failure is labeled as hypertension [115].

Social determinants of health, namely socioeconomic status, may also help explain the increased prevalence of CKD in the AA population. There is a higher proportion of AA living at lower socioeconomic status with poor access to health care, leading to late diagnosis and treatment of diseases such as DM and HTN, two major causes of CKD. In the JHS, participants who experienced the greatest decline in kidney function were older, had lower income, less education, higher systolic blood pressure, were less likely to have private insurance, and more likely to have prevalent diabetes and hypertension [116].

Paradoxically, once on hemodialysis, AA have a survival advantage over whites, likely due to multiple factors including nutritional status, inflammation, psychosocial status, and genetic variation [117-122].

Dialytic Removal of Uremic Toxins

HD is the process of removing wastes, such as uremic solutes, and extra fluid from a patient by filtering their blood through a dialyzer. Uremic solutes can be characterized as belonging to one of three groups: (1) small water-soluble compounds (< 500 Da), (2) protein bound uremic toxins (PBUTs) (most < 500 Da except leptin and retinol-binding protein), and (3) middle molecular weight molecules (≥ 500 Da) [123]. Small water-soluble compounds, such as urea and creatinine, are easily removed by dialysis and their levels can be used as markers of retention and removal by the dialysis process [124]. Middle molecules include inflammatory cytokines such as β-2-microglobulin (reduction ratio ~ 50-60%) [125], tumor-necrosis factor alpha (TNF-α), interleukin 1β, IL-6 [126]. These middle molecules are more efficiently removed by dialyzers with larger pore sized (high flux) membranes; however, these membranes do not allow passage of PBUTs such as *p*-cresol and advanced glycation end products. Although high flux membranes are somewhat effective at removing proinflammatory compounds whose retention may be implicated in CVD risk, middle molecules such as vitamin B12 and insulin can also be lost through the dialysis process [127]. Newer permeable medium cut-off (MCO) and high cut-off (HCO) membranes allow for the removal of PBUTs, while reducing the loss of albumin [128].

One of the goals of HD is to remove the excess sodium, phosphorus, and potassium that has accumulated during the interdialytic period; however, phosphorus removal during the HD procedure differs from urea or other small molecules. Water molecules bind to phosphorus, transforming this small molecule into a medium size molecule, hindering passage through the dialysis pores. Additionally, slow phosphorus transfer rates from the inaccessible intracellular

space to the accessible extracellular compartment limits removal during dialysis; therefore, serum phosphorus levels drop quickly during the first hour of dialysis, and then stabilize. An average dialysis session removes approximately 600-1200 mg of phosphorus [129, 130].

Sodium and Fluid in ESRD

HD patients are at high risk for fluid volume overload between treatments. Large fluctuations from salt and water intake between HD sessions, termed interdialytic weight gain (IDWG), result in extracellular volume expansion and elevated blood pressure, which can strain the cardiovascular system [131]. Greater sodium intake is associated with greater IDWG [132], blood pressure [131], and mortality among MHD patients [133]. To reduce IDWG, HD patients are advised to restrict their free fluid intake and reduce dietary sodium intake, which should help to decrease fluid consumption as well since salt intake leads to ‘‘osmometric thirst’’[134]. IDWG can be used to assess MHD patient compliance to salt restriction using the following rule of thumb: a 70 kg anuric patient receiving HD thrice weekly should have a mean IDWG of 1.5 kg; IDWG exceeding 1.5 kg usually represents an increase in dietary salt intake [135].

Potassium in ESRD

To prevent and manage hyperkalemia, HD patients are advised to follow a low-potassium diet, which means excluding the consumption of many plant-based foods such as nuts, seeds, beans, peas, lentils, and fruits and vegetables. Hyperkalemia may result from several non-dietary factors as well, such as metabolic acidosis or tissue breakdown, which cause a shift of K+ into the extracellular compartment. Additional contributors to hyperkalemia include prolonged fasting, medications, and insufficient potassium removal by dialysis. As an adaptation to compensate for reduced renal elimination, there is 2-3 fold higher colonic potassium excretion in HD patients;

therefore constipation, reported in ~53% of patients, may also contribute to hyperkalemia [136, 137].

Often asymptomatic, hyperkalemia can present as weakness, fatigue, palpitations, and cardiac arrhythmias. Hyperkalemia is one of the main reasons for emergency HD, and is the cause of about 2-5% of deaths among ESRD patients [138, 139].

Phosphorus in ESRD

The balance of hormonal actions that normally regulate systemic phosphorus homeostasis occur among three organs: the gut (intestinal absorption), the bone (retention or release), and the kidneys (reabsorption and excretion). This balance becomes dysregulated in ESRD and ultimately leads to impaired renal excretion and bone resorption of phosphorus, resulting in hyperphosphatemia [140]. As a result, patients receiving MHD must reduce dietary phosphorus, and are frequently prescribed phosphate binders to take with meals. However, several factors, including dietary phosphate load, vitamin D status, and phosphorus bioaccessibility, can influence intestinal phosphate absorption [141, 142]. Phosphorus in foods are found as food additives (inorganic) or naturally occurring (organic). Because organic phosphorus from plant protein sources is stored as phytate, and humans lack the degrading enzyme phytic acid, phosphorus from plant and legume derived foods is largely inaccessible, with a bioavailability < 40%. Bioavailability (or bioaccessibility) of organic phosphorus from animal and dairy protein sources is higher than from plants (about 40-60%). Inorganic phosphate additives found in processed foods have the highest bioaccessibility, estimated at 90-100% [142-144]. Additionally, the FDA does not require that manufacturers include phosphorus content on the Nutrition Facts Label [145], making it difficult for patients to estimate the amount of phosphorus contained in packaged foods. Per the 2017 KDIGO Clinical Practice Guideline Update for CKD-MBD, it is suggested that the

dietitian and other interdisciplinary staff provide education to the patient about phosphate bioavailability [146].

Treatments for Hyperphosphatemia

Dietary Phosphorus Restriction

Several dietary intervention trials have demonstrated that HD patients who reduce their intake of foods high in phosphorus or processed foods with added phosphate had significant reductions in serum phosphorus concentrations [147-149]. However, reducing phosphorus intake while ensuring adequate protein consumption can be challenging; furthermore, a restricted (and potentially imbalanced) diet can lead to unfavorable outcomes [150]. Reported nutrient intakes in HD patients instructed to follow a conventional renal diet has been associated with nutrient deficits and poor diet quality [151, 152]. Dietary phosphorus restriction limits consumption of many heart healthy foods, potentially contributing to an atherogenic dietary pattern and resulting in nutrient deficits of antioxidant vitamins such as vitamins E, C, and carotenoids [153].

Phosphorus to Protein (P/Pro) Ratio

ESRD patients require higher amounts of protein (1.0-1.2 g/kg body weight) to ensure neutral or positive nitrogen balance. Additionally, 50% of dietary proteins should be of high biological value (HBV), such as proteins derived from animal sources which provide a complete amino acid composition to promote conservation of muscle mass [154]. Given that, on average, a typical diet contains 12-14 mg of phosphorus per gram of protein, an upper limit of 10-12 mg/g can be used to identify foods with a favorable phosphorus to protein (p/pro) ratio [155]. Animal proteins can vary in their phosphorus and protein content, for instance, a whole egg contains 6 grams of protein and 86 mg of phosphorus, whereas the egg white contains 3.6 g of protein and only 5 mg of phosphorus, a p/pro ratio of less than 2 mg/gram [156]. Chicken, pork, veal, trout,

and sole have a more favorable p/pro ratio than turkey, salmon, and shrimp. A phosphorus pyramid (D'Alessandro, et. al., 2015) has been proposed as visual guide for CKD patients to identify foods based on phosphorus content, p/pro ratio, and phosphorus bioavailability. However, this pyramid is a guide for both CKD patients and ESRD patients receiving HD, and the "rules" can be somewhat confusing to follow as many foods with a favorable p/pro ratio are also foods high in potassium [157].

Phosphate Binders

In conjunction with a low phosphorus diet, phosphate binders are used to bind 250-750 mg of excess phosphorus per day for dietary phosphorus intakes of 1000 mg/d (restriction) and 1500 mg/d (typical intake), respectively. However, mean phosphorus binding capacity averages approximately 250-450 mg/day, falling short of what is required to maintain phosphorus balance [158, 159]. Despite multiple studies linking them to vascular calcification and increased risk of CVD, calcium based binders are the most commonly prescribed binder as they are well tolerated and inexpensive [160].

CKD Mineral and Bone Disorder (CKD-MBD)

In CKD Stage 3, patients may begin to develop symptoms of CKD-mineral bone disorder (MBD), a systemic condition marked by abnormal biochemical tests, vascular calcification, and alterations in bone morphology. As CKD progresses, patients can develop secondary hyperparathyroidism (SHPT) as a consequence of the excessive secretion of PTH in response to decreased calcitriol production, hypocalcemia, and hyperphosphatemia. Pharmacological treatment options include vitamin D analogs, phosphate binders, and calcimimetic agents; however, some patients will require a parathyroidectomy [161].

Vitamin D Analogues

CKD results in vitamin D deficiency (< 20 ng/mL) and insufficiency (20-29 ng/mL) due to several contributing factors, such as inadequate dietary intake and sunlight exposure, race, sex, age, obesity, and impaired renal production [162]. The main circulating form of vitamin D is collectively called calcifediol, which is commonly measured in the plasma to reflect body stores. The proximal tubular cells within the kidneys are responsible for converting calcifediol into the active form of vitamin D (1,25-dihydroxyvitamin D), calcitriol, by introducing a hydroxyl group (-OH) at the 1 position in the second hydroxylation step. The principal action of calcitriol is to promote calcium absorption from the intestine. Deficiency of calcitriol results in decreased intestinal calcium absorption, leading to secondary hyperparathyroidism characterized by hypersecretion of PTH and parathyroid gland hyperplasia. Treatment of secondary hyperparathyroidism with calcitriol can overly suppress PTH synthesis and produce hypercalcemia, which may increase risk of vascular calcification [163]. Use of vitamin D analogs that inhibit PTH gene transcription and parathyroid hyperplasia (identified as vitamin D receptor activators such as paricalcitol and doxercalciferol) have been associated with improved patient survival and reduced vascular calcification and inflammatory status [164-166].

Calcimimetic Agents

For those patients who do not respond to phosphate binders and vitamin D analogues for SHPT treatment, calcimimetic agents, such as Cinacalcet HCl, can be used. As allosteric activators of the calcium sensing receptor (CaSR) in the parathyroid glands and other tissues, calcimimetics suppress PTH secretion [167]. These agents can be prescribed in combination with vitamin D analogues.

Cardiovascular Complications From Hyperphosphatemia

For ESRD patients on HD, several studies have reported an independent association between hyperphosphatemia and both cardiovascular and all-cause mortality [168, 169]. Ganesh, et. al. found a higher mortality risk among HD patients with high serum phosphorus (> 6.5mg/dL) compared to those with a lower serum phosphorus (≤ 6.5mg/dL) (RR 1.4, $p < 0.0005$) [170].

Hyperphosphatemia has also been independently associated with coronary artery and aortic calcification, where each one mg/dL increase in serum phosphorus corresponds to the same increase in calcification associated with 2 ½ years of receiving dialysis [38, 171].

In a retrospective cohort study of 139,328 HD patients followed from July 2001 to June 2006, investigators found that AA receiving the highest doses of paricalcitol (> 10mg/week) had a survival advantage over nonblacks who received lower doses or no vitamin D. When compared to nonblacks, hyperparathyroidism and hypercalcemia, *but not serum P*, were more prevalent among the AA patients. As a result, AA-HD patients were more likely to receive higher doses of vitamin D analogs than nonblacks [172]. In a study published in 2011, researchers conducted 630 bone biopsies in HD patients, finding that white patients demonstrated predominantly low bone turnover (62%), whereas black patients exhibited mostly normal or high turnover (68%). Given patients with low bone turnover have abnormal calcium homeostasis [173], and low bone turnover is associated with vascular calcification [174], differences in mineral metabolism between ethnicities, such as PTH resistance in the black population, may contribute to the survival advantage observed in the AA HD population [175].

In addition to better mineral density and bone architecture, AA HD patients have a lower prevalence of coronary artery and aortic valve calcification and fewer myocardial infarctions as compared with non-blacks [38, 176-179]. Among non CKD populations, AA (as compared to

those of European ancestry) have lower levels of calcified atherosclerotic plaque even though they experience more severe traditional CVD risk factors such as HTN, poor glycemic control, and higher prevalence of dyslipidemia with higher overall mortality rates from CVD [180-182].

Renal Diet and Antioxidant Intake

Although both the dialysis procedure and pharmacological treatments are effective at reducing the uremic toxin load, restrictions on dietary phosphorus and potassium are often required to maintain serum levels within physiological range [183]. In an effort to avoid foods high in phosphorus and potassium, limits are placed on the quantity of certain fruits, vegetables, nuts, legumes, dairy, and whole grains that can be eaten [184]. This reduced consumption of foods naturally rich in phytochemicals, such as carotenoids and polyphenols, can result in a loss of benefit from the antioxidant and anti-inflammatory activities associated with their intake [185].

Dietary Patterns in ESRD

Nutrition research has shifted focus from single nutrients or foods to dietary pattern analysis, which describes the overall diet and their combination, frequency, and quantity with the association on health risk [147, 186-188].

Most studies which examine dietary patterns focus on prevention of disease progression. It has been found that dietary patterns high in fat and sugar, considered “unhealthy”, are associated with increased risk and progression of comorbidities such as heart disease, diabetes, and CKD [189-191], whereas healthier diet patterns, which include higher intakes of vegetables, fruits, legumes, nuts, whole grains, fish, and low-fat dairy, and lower intakes of red and processed meats, sodium, and sugar-sweetened beverages, have been associated with a lower incidence of CKD [26].

Only a few dietary pattern studies have focused on the HD population. Sualeheen, et. al, found that for Malaysian HD patients, dietary patterns reflective of home-based, healthier food

choices were associated with better nutritional status [192]. In the Japan Dialysis Outcomes and Practice Patterns Study (JDOPPS), an "unbalanced" dietary pattern was associated with increased CVD related hospitalization and all-cause mortality [193]. However, in a European cohort of patients enrolled in the DIET-HD study, a dietary pattern high in fruits and vegetables was not associated with a cardiovascular or all-cause mortality benefit [194]. It is worth noting that the diet analyses used in both the JDOPPS and DIET-HD studies were based on self-reported food frequency questionnaires, which did not account for differences in portion sizes.

Two main analytical approaches used to identify dietary patterns in nutritional epidemiology are *à priori* (hypothesis-driven) and *à posteriori* (data-driven) methods [195, 196]. *À priori* methods are based on indices of diet quality or nutritional health defined scores and assess the extent to which a subject complies with the predefined dietary pattern, whereas *à posteriori* methods use multivariate statistical techniques to derive dietary patterns empirically based on the actual diet in a specific population [197].

À Priori Methods

À priori methods are usually based on dietary guideline definitions and employ a scoring algorithm to determine participant adherence. Examples of *à priori* dietary patterns include the Mediterranean Diet Score [198], the Healthy Eating Index [199], and the Dietary Inflammatory Index (DII) [200]. These methods are based on indices of diet quality or presence or absence of certain foods or nutrient characteristics used to calculate a score, which is then operationalized as an explanatory variable [201].

The DII is an *à priori* method developed by researchers at the University of South Carolina to provide a means for estimating the overall inflammatory potential of the diet [202]. The DII is based upon the inflammatory properties of macronutrients, vitamins and minerals, flavonoids, and

other bioactive compounds and includes evidence from both *in vitro* and *in vivo* experiments, as well as several study designs, nutritional assessment methods, and populations. The DII differs from other epidemiologic dietary indices, such as DASH or HEI, which are based on adherence to dietary guidelines or recommendations [203].

The current DII uses a scoring algorithm standardized to the distribution of dietary intake from representative populations around the world of 45 food parameters based on their inflammatory effect on six biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein). Higher DII scores indicate more pro-inflammatory diets, whereas negative values reflect anti-inflammatory diets, with scores potentially ranging from +7.98 (pro-inflammatory) to -8.87 (anti-inflammatory) [202].

As chronic low-grade inflammation is both a consequence and contributor to CKD [204] and diet has the potential to modulate inflammation [205], assessing the DII for HD patients may provide valuable insight into the potential inflammatory contribution from foods consumed in a typical renal diet.

À Posteriori Methods

Two commonly used *à posteriori* methods are (1) cluster analysis, which separates individuals into mutually exclusive, non-overlapping groups based on differences in mean dietary intake [197] and (2) factor analysis, which reduces data based on correlation or covariance matrices into components, factors, or patterns based upon relationships between dietary items [206]. These methods are driven by the underlying dietary data and summarize the effect of the overall diet. Rather than assessing the relationship of health with single nutrients, using dietary patterns reflects the synergistic impact that habitual patterns of foods eaten in combination has on health outcomes.

Cluster analysis is a common *à posteriori* method used to assess dietary patterns through a data reduction technique [207].

Patient Reported Outcome Measures (PROMs)

Diet Data

In the clinical setting, formal methods of dietary assessment are seldom used, due to time constraints and patient loads. However, in research, either food frequency questionnaires or dietary recalls (24 hour, 2 or 3 days) are used to collect diet data. With diet recalls, issues can arise from underreporting usual energy intake which can include both under-recording and undereating. This former group is also referred to as implausible low energy intake (EI) or "low-energy reporters". In under-recording, participants either fail to report all the items consumed or underestimate the amounts reported leading to a discrepancy between reported EI and measured energy expenditure (EE). In undereating, participants eat less than required to maintain body weight, which is accompanied by a decline in body mass [208].

To account for under-recording, several methods are available to remove biologically implausible intake reports before drawing conclusions about diet associations. Some methods are crude, such as excluding only those participants reporting EI extremes, whereas others take into consideration activity level and employ cutoffs using statistical adjustments that account for within-participant variation in EI and total energy expenditure (TEE) [209].

Quality of Life (QOL)

The Kidney Disease Quality of Life Short-Form 36-items survey (KDQOL-SF36™) is a validated self-reported questionnaire developed to assess quality of life for ESRD patients on HD [210]. As part of its conditions for coverage, CMS mandated that ESRD facilities conduct an annual assessment of health related quality of life (HRQOL) on all dialysis patients [211, 212]. KDQOL™-36 was chosen as the HRQOL required survey by The National Quality Forum as the

tool of choice. Dialysis facilities are required to assess patients' HRQOL within 4 months of initiating dialysis, and annually thereafter [213]. The survey is comprised of five subscales calculated separately: 1) SF-12 physical component summary (PCS), 2) SF-12 mental component summary (MCS), 3) burden of kidney disease, 4) symptoms of kidney disease, and 5) effects of kidney disease. Subscale scores range from 0 to 100, with lower scores indicating poor self-reported QOL [214]. Independent of demographic and comorbidity factors, lower PCS and MCS subscale scores have been associated with higher risk of hospitalization and death in HD patients. Several studies have found SF-12 PCS to be the strongest prognostic subscale [215, 216]. Additionally, lower PCS and MCS subscale scores were found to be positively correlated with both Body Mass Index (BMI) and body fat percentage [217]. Common symptoms of ESRD include lack of energy or fatigue, pain, drowsiness, pruritis, dry skin, shortness of breath, swelling of the legs and arms, worrying, nervousness, irritability, and sadness. In the month preceding death, symptom burden has been reported to be the greatest, and persistent fluid overload and lethargy have been found to be indicators of near death [218].

Appetite Diet and Assessment Tool (ADAT)

A 44 question appetite diet and assessment tool (ADAT) was initially developed for the National Institutes of Health Reduction of Morbidity and Mortality in HD Patients Pilot study to evaluate appetite and factors affecting dietary intake [219]. The first three questions from the ADAT were later used to determine whether appetite had changed over time in the treatment groups for patients participating in the Hemodialysis (HEMO) study. It was found that poor appetite was associated with increased hospitalization rates among HD patients [220].

Biological Outcome Measures

Biochemical Markers

Per CMS guidelines, HD facilities must evaluate factors associated with anemia (i.e. hemoglobin, hematocrit, and iron stores), evaluate nutritional status by monitoring albumin levels and body weight at least monthly, and assess the adequacy of the patient's dialysis prescription at least monthly to meet a minimum Kt/V goal of at least 1.2 [221]. In addition to these federal requirements, KDOQI guidelines recommend monitoring serum calcium, phosphate, and PTH for the diagnosis, evaluation and treatment of CKD-MBD. [222]. Additional markers, such as serum creatinine levels, may be monitored. As a breakdown product of creatine phosphate in muscle, high levels of creatinine (in HD patients without residual renal function) may serve as a surrogate of muscle mass and have been associated with better survival predictability [223, 224].

Anthropometry

Anthropometric measurements, such as height, weight, BMI, body circumferences, and skinfold thickness are quantitative measurements used to assess body composition. Although obesity is associated with both a higher risk of developing CKD [225] and increased CV mortality in the general population [226], once a patient develops CKD, overweight and obesity are paradoxically associated with a survival benefit, irrespective of race [227-229], with the most prominent survival advantage among AA MHD patients compared to Hispanics and non-Hispanic Whites [228, 230]. This 'obesity paradox' may be related to uremic toxin sequestration in fat mass, lipoprotein defense against circulating endotoxins, reduced prevalence of protein energy wasting (PEW), increased micronutrient intake, attenuation of inflammation, additional "reserve" during times of illness, or an interplay of several factors [231, 232].

Even though both higher fat mass and muscle mass are associated with improved survival, muscle mass appears to be superior to fat mass in providing greater mortality benefits [233]. In

comparison to fat mass gains, achieving muscle gains (or preventing losses) is more difficult, requiring both resistance exercise along with a high protein intake of HBV [234]. The survival benefit observed in AA ESRD patients may be related to muscle mass, which is higher in AA than in Whites [233, 235].

Given treatments aimed at traditional risk factors such as obesity, hypertension [236] and hypercholesterolemia [88] have not been shown to reduce CVD morbidity and mortality in ESRD patients, and maintaining lean body mass has been shown to confer a survival benefit, dietary intervention efforts focused on this latter goal may be efficacious.

Measuring Fat Mass and Lean Body Mass

BMI cannot distinguish between fat mass and lean body mass (LBM), which represents muscle mass and somatic protein stores in HD patients [224]. Evaluating the combination of both fat tissue index and skeletal muscle mass index has been reported to more accurately predict all-cause mortality when compared with BMI [237]. Several body composition methods are available, such as dual-energy X-ray absorptiometry (DEXA), the gold standard for fat mass assessment, and bioimpedance analysis (BIA), a less expensive and more portable option to assess fat and fat free mass [238]. Indirect measurements, such as mid-arm muscle circumference (MAMC) and hand grip strength (HGS) can serve as a surrogates for LBM in HD patients and have been widely used in epidemiological studies [223].

NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI)

Published in the American Journal of Kidney Diseases (AJKD), The National Kidney Foundation (NKF) produces evidence-based clinical practice guidelines through the NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI)™ [239] and published the most recent nutrition guidelines in 2000 [154]. Current nutrition guidelines for HD patients per the *5th Edition*

Pocket Guide to Nutrition Assessment of the patient with Chronic Kidney Disease are outlined in Table 1 [240].

KDOQI, in collaboration with the Academy of Nutrition and Dietetics (AND), is in the process of updating its Clinical Practice Guideline on Nutrition in CKD which is still undergoing revisions based on public commentary [239]. The draft, available for review, introduces changes to several key guidelines and an expanded methodology used in the creation of the new guidelines. Both a workgroup of 15 members, including physicians, Registered Dietitians, researchers, and methodologists with expertise in the renal nutrition field, and an evidence review team worked together to develop these updated CKD specific nutrition guidelines by following the AND's systematic review methodology. Proposed changes to the new guidelines for HD patients include a slight reduction in dietary energy intake (DEI) and dietary protein intake (DPI) ranges, without mention of the specific need for high biological value [25].

The importance of diet to clinical outcomes is of such significance that CMS has mandated that every dialysis patient should receive individualized comprehensive assessment and treatment by a renal dietitian [221]. With advanced kidney disease, patients may become deficient in B vitamins, iron, vitamins C and K, zinc, copper, selenium, and calcitriol. Inadequate micronutrient intakes can contribute to the higher burden of oxidative stress, inflammation, and CVD observed in the ESRD population [241]. Conversely, excessive intakes of phosphorus, potassium, and fluid are also associated with increased risks of cardiovascular morbidity and mortality [138, 242, 243]. Nutrient guidelines are often communicated to patients using written materials which highlight foods to avoid or include based on sodium, potassium, and phosphorus content. Recently, attention has shifted from restricting all high phosphorus containing foods to limiting those foods high in inorganic, and thus highly bioavailable, phosphorus [157, 184, 244].

The Role of the Registered Dietitian Nutritionist (RDN)

Registered Dietitian Nutritionists (RDNs) must adhere to a code of ethics which requires using current evidence based nutritional guidelines. Patient-client centered care is a major tenet of the interactive-integrative paradigm. The RDN utilizes both information obtained from the patient, which not only includes access to food, barriers (financial, food insecurity, and motivational), family support, reported intake, and self-efficacy for behavior change, with clinical history to guide medical nutrition therapy (MNT) [245]. When discussing with the patient foods that should either be included or excluded from the diet, several foods may fall into a "grey" area. For example, whole grains, legumes, fruits, and vegetables provide good sources of fiber which can help alleviate constipation, yet many of these foods are high in phosphorus and potassium [246].

Controversial Foods

The egg exemplifies a type of "controversial" food for the HD patient, as it provides a readily available, inexpensive source of protein, yet is high in phosphorus (albeit organic), and a rich source of cholesterol. Further research into the current recommendations for eggs in the CKD population revealed a lack of both formal guidelines and published studies; therefore, we completed the first published review (Tallman, et. al, 2018) examining egg intake in CKD [247].

Despite several meta-analyses suggesting that higher egg consumption of up to one egg per day is not associated with increased CVD risk in the general population [248, 249], egg intake remains controversial, notably for individuals with comorbidities, such as diabetes and ESRD, as CVD risk and consumption of whole fresh eggs remains inconclusive for these populations [250, 251].

The egg yolk contains bioactive compounds, including lutein, zeaxanthin, and vitamin D, nutrients which may be beneficial for HD patients. However, the yolk is also a rich source of both cholesterol and phosphorus. Whole egg consumption in context of the entire diet, particularly when

compared to foods an egg may replace, such as processed foods or high sugar products, should be examined given individuals do not consume nutrients or foods in isolation.

Optimal Renal Diet

Traditionally, nutrition research has focused on health outcomes with individual nutrients and foods, such as eggs and CVD risk; however, using this approach has several limitations. First, people eat meals which contain a variety of ingredients with complex combinations of nutrients that may act synergistically. Second, the effect of a single nutrient may be difficult to discern, but the cumulative effects of several nutrients in a dietary pattern may be large enough to detect. Third, intercorrelation among some nutrients makes it difficult to examine their separate effects. These limitations can be overcome by using a dietary pattern approach to examine how foods and nutrients are eaten in combination [187].

Nutritional approaches to improve outcomes for ESRD patients on HD have evolved over time and reflect technological advances in RRT [252]. At the same time, nutritional epidemiologic studies have shifted to using a dietary pattern analysis to examine associations with health outcomes. The changes proposed by the updated KDOQI guidelines reflect this paradigm shift. The current draft includes a statement on dietary patterns suggesting a Mediterranean diet for adult CKD 1-5 (non-dialysis) patients to improve lipid profiles. Presently, there are no suggested patterns for AA ESRD patients receiving HD.

Specific Aims

Based on the preceding sections, the *long term goal* of research in this field is to optimize nutrition regimens in HD patients to improve health outcomes.

The *central hypothesis* is that renal dietary guidelines need to be targeted based on patient-centered dietary patterns. The *rationale* for this research is that once specific dietary patterns are

identified, cross-sectional studies can be designed to evaluate health outcomes. The goal of this Ph.D. project is to identify and document dietary patterns in *African American* HD patients.

To test my hypothesis the following *specific aims* were established:

Specific Aim One: To Characterize the Nutrition and Health Status in a Cohort of African American Maintenance Hemodialysis Patients.

- Specific Aim 1A: To Characterize the Overall Study Population.
- Specific Aim 1B: To Assess Protein Energy Wasting (PEW), Dyslipidemia, and Inflammation in the Study Population.
- Specific Aim 1C: To Evaluate Phosphorus to Protein Ratio and Dietary Inflammatory Index From the Derived Nutrition Information.

Specific Aim Two: To Evaluate the Association of Cluster Analysis Derived Dietary Patterns with Health Outcomes in a Cohort of African American Maintenance Hemodialysis Patients.

Specific Aim Three: To Assess the Effect of Nutrition and Health Status in a Cohort of African American Maintenance Hemodialysis Patients on Mortality.

Tables and Figures

Table 1**:** Nutrient Recommendations for HD Patients

Protein (g/kg)	1.2 stable 1.2-1.3 acutely ill or PEW
Energy (kcals/kg)	30-35 ≥ 60 years 35 < 60 years
Sodium (mg/d)	750-2000
Potassium (mEq/d)	Up to 70-80 mEq/d; adjust to serum levels
Fiber g/d	20-25
Fluids cc/d	750-1500
Calcium mg/d	≤ 1000; maintain serum calcium WNL
Iron mg/d	Individualized
Magnesium mg/d	200-300
Phosphorus mg/d	10-17 mg/kg/d
Selenium mcg/d	NA
Zinc mg/d	15
Daily Vitamin Supplementation Recommendations	
Ascorbic Acid mg/d	75-90
B_1 (Thiamine) mg/d	RDA
B_2 (Riboflavin) mg/d	RDA
B_6 (Pyridoxamine) mg/d	10
B_{12} (Cobalamin) µg/d	RDA
Biotin µg/d	RDA
Folic Acid mg/d	1
Niacin mg/d	RDA
Pantothenic Acid mg/d	RDA
Vitamin A µg RE/d	None
25-hydroxy Vitamin D IU	Calcitriol, vitamin D analogs, calcimimetics based on serum calcium, phos
Vitamin E (IU)	15
Vitamin K µg/d	With antibiotic therapy, 10 mg/d

mg = milligrams; RDA = recommended dietary allowance

Table 2: Criteria for the Clinical Diagnosis of PEW in CKD

Serum Chemistry	Serum albumin < 3.8 g/dl[a] Serum prealbumin (transthyretin) < 30mg/dl[a] Serum cholesterol < 100mg/dl[a]
BMI	BMI (edema-free) < 23 Unintentional weight loss over time: 5% over 3 months or 10% over 6 months Total body fat percentage < 10%
Muscle Mass	Reduced muscle mass 5% over 3 months or 10% over 6 months Reduced mid-arm muscle circumference area[b] (reduction > 10% in relation to 50th percentile of reference population) Creatinine appearance[c]
Dietary Intake	Unintentional low dietary protein intake < 0.80g/kg/day for at least 2 months Unintentional low dietary energy intake < 25kcal/kg/day for at least 2 months

Adapted from Obi, et. al. *Curr Opin Clin Nutr Metab Care,* 2015 [96].

At least three of the four listed categories along with at least one test in each of the selected categories must be satisfied for the diagnosis of kidney disease related PEW. Each criterion should be documented on at least three occasions, preferably 2–4 weeks apart.

Not valid in abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines

[b]Measured by a trained anthropometrist.

[c]Creatinine appearance is influenced by both muscle mass and meat intake.

Table 3**:** EWGSOP2 Sarcopenia Cut-Off Points

Test	Cut-off points for men	Cut-off points for women
Sarcopenia cut-off points for low strength by chair stand and grip strength		
Grip strength	**< 27 kg**	**< 16 kg**
Chair stand	**> 15 s for five rises**	
Sarcopenia cut-off points for low muscle quantity		
ASM	**< 20 kg**	**< 15 kg**
ASM/height^2	**< 7.0 kg/m^2**	**< 5.5 kg/m^2**
Sarcopenia cut-off points for low performance		
Gait speed	**≤ 0.8 m/s**	
SPPB	**≤ 8 point score**	
TUG	**≥ 20 s**	
400 m walk test	**Non-completion or ≥ 6 min for completion**	

Table adapted from *Sarcopenia: revised European consensus on definition and diagnosis* **[102]**. ASM: Appendicular Skeletal Muscle Mass; SPPB: Short Physical Performance Battery; TUG: Timed-Up and Go test

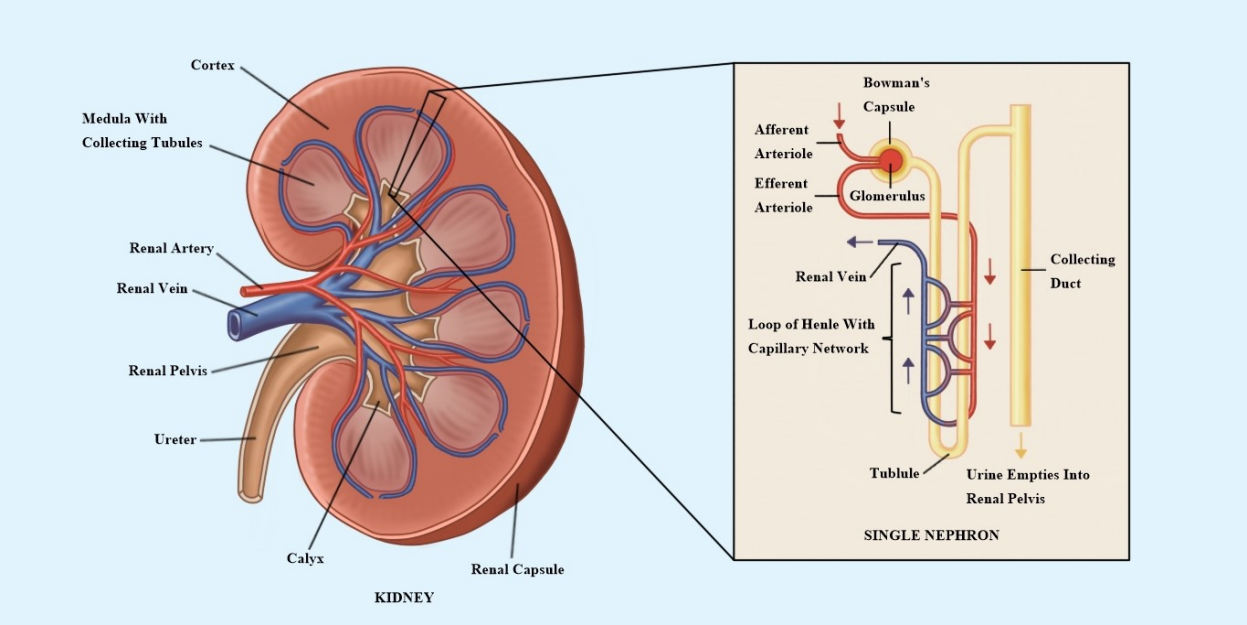


Figure 1: Anatomy of the Kidney and Nephron (adapted from National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases) [3]

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent Albuminuria Categories Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g	30-300 mg/g	> 300 mg/g
GFR Categories (mL/min/1.73m^2) Description and Range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mild to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	< 15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 2: Prognosis of CKD by GFR and Albuminuria Category [17]

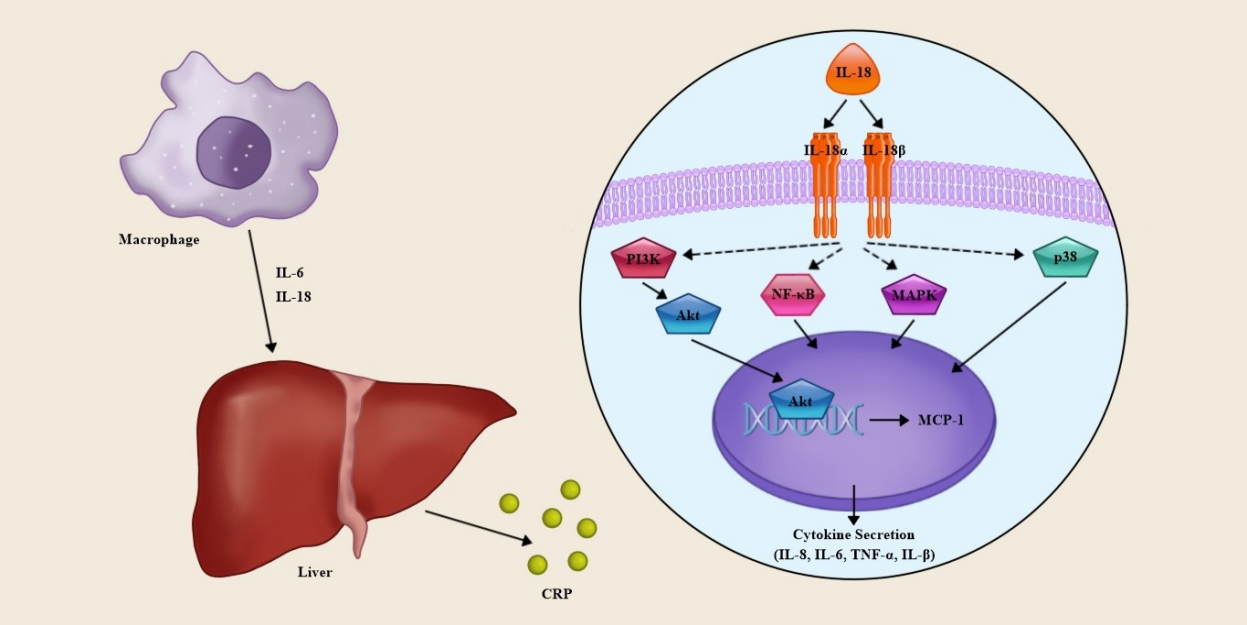


Figure 3: IL-18 Pathway and Downstream Cytokines

Table 26. Therapeutic Lifestyle Changes (TLC) for Adults with Chronic Kidney Disease.

Diet (Consult a dietitian with expertise in chronic kidney disease)
Emphasize reduced saturated fat:
Saturated fat: <7% of total calories
Polyunsaturated fat: up to 10% of total calories
Monounsaturated fat: up to 20% of total calories
Total fat: 25%-35% of total calories
Cholesterol: <200 mg per day
Carbohydrate: 50%-60% of total calories
Emphasize components that reduce dyslipidemia
Fiber: 20-30 g per day emphasize 5-10 g per day viscous (soluble) fiber
Consider plant stanols/sterols 2 g per day
Improve glycemic control
Emphasize total calories to attain/maintain standard NHANES body weight
Match intake of overall energy (calories) to overall energy needs
Body Mass Index 25-28 kg/m^2
Waist circumference
Men <40 inches (102 cm)
Women <35 inches (88 cm)
Waist-Hip Ratio (Men <1.0; women <0.8)
Physical Activity
Moderate daily lifestyle activities
Use pedometer to attain/maintain 10,000 steps per day
Emphasize regular daily motion and distance (within ability)
Moderate planned physical activity
3-4 times per week 20-30 minute periods of activity
Include 5-minute warm-up and cool-down
Choose walking, swimming, supervised exercise (within ability)
Include resistance exercise training
Emphasize lean muscle mass and reducing excess body fat
Habits
Alcohol in moderation: limit one drink per day with approval of physician
Smoking cessation

References[3;30;284;286-288] See also Appendix 2.
Abbreviation: NHANES, National Health and Nutrition Examination Survey.

Figure 4: Therapeutic Lifestyle Changes (TLC) for Adults With Chronic Kidney Disease From KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease [89]

CHAPTER 2: METHODOLOGY

General Study Design

Data was collected from subjects participating in the Palm Tocotrienols in Chronic Hemodialysis (USA) (PATCH) Study (NCT02358967), a randomized double-blind, placebo-controlled trial evaluating the effects of daily supplementation with 300 mg of a vitamin E tocotrienol-rich fraction (TRF) on markers of inflammation, oxidative stress, and blood lipids in MHD patients. The PATCH clinical trial is a multinational cohort of patients receiving MHD and includes a Malaysian arm (NCT02913690) (Figure 5).

The purpose of this study is to analyze the impact of dietary patterns with health outcomes in African American patients receiving MHD. To achieve this goal, a secondary analyses of data collected from 135 subjects participating in the PATCH Study was conducted. Given the small percentage of non-African American subjects (5%) in the cohort, only AA subjects were considered for inclusion in this secondary study. Baseline data was used for all analyses, with the exception of diet data, for which the average of six 24-hr dietary recalls taken during the duration of the study were used. 27 AA subjects for whom all six 24-hr dietary recalls were deemed implausible were screened out, and 101 AA subjects with plausible dietary intake records were included in all subsequent analyses.

Criteria for study participation included: (1) Patient is willing and able to give informed consent for participation in the trial (2) Male or female, aged 18 years and above and undergoing chronic hemodialysis treatment for more than 3 months (life expectancy > 1 year). (3) Able and willing to comply with all trial requirements.(4) Willing to allow his or her Physician, Nephrologist, or General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

Exclusion criteria included (1) Participants who have participated in another research trial involving an investigational product in the past 12 weeks. (2) History of functional kidney transplant 6 months before study entry; anticipated live donor kidney transplant over the study duration. (3) Participants who are taking vitamin E- containing supplements > 60 IU/d during the past 30 days. (4) History of poor adherence to hemodialysis or medical regimen. (5) Participants who are currently on active treatment for cancer, excluding basal cell carcinoma of the skin. (6) Participants who have been diagnosed with HIV/AIDS and/or on anti-HIV therapy. (HIV seropositivity is not an exclusion criterion). (7) Patients taking anti-inflammatory medication, except aspirin < 325 mg/d, over the past 30 days. (8) Female participants who are pregnant, lactating or planning pregnancy during the course of the trial. (9) Participants who are receiving nutritional support (i.e. enteral and intra-venous route). (10) Patients using a temporary catheter for dialysis access at baseline or patients receiving a graft/fistula within the 6-month study period. (11) More than two hospitalizations within the last 90 days or one hospitalization within the 30 days preceding enrollment. (12) Any other significant disease or disorder which, in the opinion of their nephrologist, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

135 subjects were enrolled from five hemodialysis clinics in the metro Detroit, Michigan (USA) area and randomly assignment to receive either treatment or placebo. Three DaVita clinics (Redford, Highland Park, and Kresge), two Henry Ford clinics (Fairlane and West Pavilion) and one private clinic, Great Lakes Dialysis, participated in the study. Participants were enrolled in the study for 15 months (12 month treatment period, followed by a 3 month washout period with 3 month follow-up) and visited quarterly. Dates of enrollment spanned from June 2017 to February 2018 with all study procedures completed by April 2019.

Ethics and Human Subject Issues

The study was approved by the ethics boards of participating dialysis units and Wayne State University's Institutional Review Board. All subjects provided informed written consent. Informed consent was obtained by either the Nephrologist or the Registered Dietitian at each clinic site. Study participants received $15 compensation monthly for the first 12 first months of enrollment while receiving capsules, and an additional $20 for completing the entire study (i.e. participating in the 15 month follow-up visit).

Capsule Distribution

At the Great Lakes and DaVita clinics, participants were provided capsules by the nursing staff during dialysis days (three days per week) under direct observation, and were responsible to self-administer capsules on non-dialysis days. At the two Henry Ford Clinics, participants were responsible for capsule self-administration on all days. A member from the PATCH clinical team was responsible for distributing the capsules to the clinic staff for disbursement, and solely responsible for disbursing participant compensation (in the form of a gift card) and obtaining the participant's signature as proof of receipt.

Collection and Handling of Blood Samples

Two 10 mL vacutainer tubes with Ethylenediaminetetraacetic acid (EDTA) and lithium heparin preservatives (BD, Franklin Lakes, NJ, USA) were labeled with the patient name and instructions on pre-dialysis blood draw and delivered to the floor charge nurse. Clinic dialysis technicians collected pre-dialysis blood samples from patients prior to their dialysis session and placed the samples into sealed specimen bags under refrigeration. A member from the PATCH clinical team relabeled the tubes with the WSU identification number, packed the samples on ice, and transported them to a Wayne State University laboratory within two hours of collection. Samples collected in the EDTA tubes were designated for analyses of lipid profiles while lithium

heparin tubes were used for analyses of inflammatory markers. Plasma was separated by centrifugation at 3500 rpm for 10 minutes at 4°C (GS-6KR Centrifuge, Beckman-Coulter, USA) and aliquots were stored at -80°C until further analysis.

Patients Demographics and Biochemical Data

A case report form (Appendix A) was used to collect data provided by the HD clinic. Demographic data, recent laboratory values, diagnoses, dialysis vintage, prescribed medication, hemodialysis prescription, and measures of dialysis adequacy were obtained from both the medical chart and from clinic staff via printouts from the electronic medical record. Additional information that was not available in the clinic chart was obtained from the patient. The data from these records were transposed by hand to the case report form to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule to protect the patients' personal health information (PHI). All data was then entered manually into an excel program, using a Wayne State number to identify each patient.

Patient Reported Outcome Measures (PROMs)

24-hour dietary recall

Six 24-hour dietary recalls (Appendix A) taken on non-dialysis days were collected in person quarterly over a 15-month time period [207, 253] using the U.S. Department of Agriculture (USDA) five-pass method [254]. Household measuring cups and spoons were used as a visual aid to assist subjects in gauging portion sizes. All 24-hr dietary recalls were collected by a single Registered Dietitian to eliminate inter-observer variation. Interviews were conducted at each clinic during the dialysis session. The dietary recalls were then manually entered into the Food Processor SQL software package (version 11.2, 2016, ESHA Research, Salem, OR) to calculate nutrient analyses and to generate reports for all collected recalls (Appendix C).

Implausible Dietary Intake Reports

To reduce the effect of confounding from physiologically implausible reported energy intakes (rEI), dietary reports from both over and under-reporters were screened out [255]. Using the method introduced by McCrory, et al., which accounts for within-subject errors in rEI and predicted total energy expenditure (pTEE) without estimation of physical activity level, a 2-standard deviation cutoff was used to classify 24HR recalls less than 56% or more than 144% of estimated energy needs as implausible using the following equation.

$$\pm 2\sigma = \sqrt{\frac{CV_{wEI}^2}{d} + CV_{wpTEE}^2 + CV_{tmTEE}^2}$$

where CV_{wEI} is the within-subject coefficient of variation in energy intake, d is the number of days of energy intake measurement, the pTEE prediction equation as follows:

$$pTEE = 7.377 - (0.073 \times age) + (0.0806\, x\, weight) + (0.0135 \times height) - (1.363\, x\, sex),$$

where age is in years, weight is in kg, height is standing height in cm, and sex is 0 for men and 1 for women. The CV_{wEI} was calculated at 25.7% with 6 days (d) of energy intake measurements. A value of 17.7% was used for CV_{wpTEE} , which is the coefficient of variation (CV) of pTEE, and 8.2% was used for CV_{tmTEE}, which is the within-person CV of measured TEE which takes into account measurement error and biological variation in TEE. These latter two values are constants derived from previous studies [209, 256]. Edema-free adjusted body weight (aBW_{ef}) was used for patients whose weight was < 95% or > 115% of standard body weight (SBW) using the following equation [154, 257]:

$$aBW_{ef} = BW_{ef} + [(SBW - BW_{ef})\, x\, 0.25],$$

where SBW is defined as the 50th percentile of body weight for gender, height and body frame size determined from the National Health and Nutrition Examination Survey (NHANES) II data [258]. After removing 27 subjects for whom all six dietary recalls were considered implausible, a total sample size of n = 101 was used for all subsequent analyses.

Dietary Inflammatory Index

29 food parameters were available from all plausible dietary intake records, including mean daily intakes of energy, protein, carbohydrate, fat, saturated fat, polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), omega-3 fatty acids, omega-6 fatty acids, trans fats, cholesterol, vitamin A, beta-carotene, vitamin E, vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, vitamin D, magnesium, iron, zinc, selenium, fiber, alcohol, and caffeine were used for the calculation of DII. The inflammatory effect scores used for calculation of the DII is shown in Table 4. A z-score for each food consumed was calculated by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of "right skewing", this value was then converted to a centered percentile score. The centered percentile score for each food parameter was then multiplied by the respective food parameter effect score to obtain a food parameter-specific DII score for a given participant. The overall DII score for each subject was calculated by summing all food parameter DII scores for that subject; the mean DII scores from all plausible recalls were used in subsequent analyses. DII scores were dichotomized and treated as an independent categorical variable from which to compare differences in higher and lower DII with inflammatory markers, clinical chemistry, and dietary intake.

Cluster Analysis Derived Dietary Patterns

A flowchart depiction is shown in Figure 6. Using Microsoft excel, for each subject, foods consumed at each timepoint for all plausible intake records were compiled. Household measurements were converted to gram weights for all foods using the USDA Nutrient database, nutrient analysis listed on web sites by restaurants, fast food establishments, or manufacturer provided information. The gram weights were cross checked with the nutritional analysis output from ESHA Food Processor SQL software package. All individual foods recorded for all subjects were combined into one excel sheet and sorted by name to identify core food groups based on conceptual and compositional similarities. Identifying groups of food items requires an understanding of food preparation practices, food composition, and patterns of consumption. For instance, breads were subdivided into yeast breads and quick breads, since chemical leavening agents are used in the latter product, and these agents are sources of inorganic phosphorus. Thirty-three food groups were identified. A template was created to (1) sort all foods recorded from the 24-hr dietary recalls into each of the respective thirty-three food groups by gram weight and (2) calculate the mean intake of each food group per subject. Frequency distribution was calculated for all food groups to determine if any food group was consumed with less than a 5% frequency. Since no foods groups met that criteria, all thirty-three food groups were converted to percent contribution of total daily energy (%TE) intake [259]. A cluster analysis was performed using the *k*-means algorithm, a nonhierarchical clustering method which classifies participants into non-overlapping groups based on Euclidean distance, to obtain dietary patterns. A two cluster membership was found to provide the optimal solution. Convergence was achieved after seven iterations with a membership of n = 47 in cluster 1 and n = 54 in cluster 2. ANOVA revealed significant differences between groups for six variables ($\alpha = 0.10$). A second cluster analysis was

conducted with only the six significant variables. A Chi-Square test of homogeneity was conducted to determine discordant pairs. Percent concordance between all variables and all significant variables was 84.2% ($\kappa = 0.674$); therefore, all variables were included in the dietary pattern analyses.

Statistical Analyses

Differences between groups were compared according to data distribution using t test or Mann-Whitney U test for continuous variables and Pearson chi-square test for categorical variables. For all tests, the level of significance was set as $p < 0.05$. All analyses were performed using SPSS (Version 25, SPSS Inc., Chicago, Illinois, USA).

Appetite and Diet Assessment Tool (ADAT)

Responses were recorded to the three question ADAT for all subjects participating in the PATCH study on a quarterly basis (Appendix A).

Kidney Disease Quality of Life Short-Form 36-items survey (KDQOL-SF36™)

KDQOL questionnaires (Appendix C) were administered to participants for both Henry Ford and DaVita clinics. Although the KDQOL is designed to be a self-administered questionnaire, given the low literacy rate of the enrolled subjects, it was determined that the questions be read and responses recorded by a member from the PATCH clinical team. A stand-alone excel scoring tool developed by the KDQOL Working Group was used to score all surveys [214].

Biochemical Outcome Measures

Lipid Profiles

Plasma TC and triglycerides (TAG) were determined by enzymatic assays (Pointe Scientific Inc, Canton, MI, USA). High density lipoprotein cholesterol (HDL-C) was measured in the supernatant after precipitation of apoB-containing lipoproteins by dextran sulfate and magnesium ions (Pointe Scientific Inc, Canton, MI, USA). Low density lipoprotein cholesterol

(LDL-C) was calculated using the Friedwald equation by difference (LDL-C = TC – HDL-C − TAG/5). HDL and LDL subfractions from plasma were also measured via polyacrylamide gel electrophoresis using the Lipoprint™ System (Quantimetrix Corporation, Redondo Beach, CA, USA). Using the manufacturer's proprietary software, HDL and LDL subfractions were quantitated after electrophoresis. Both HDL and LDL were then grouped into large buoyant, intermediate lipoproteins, and small-dense lipoproteins. The Lipoprint™ system is U.S. Food and Drug Administration (FDA) certified for LDL measurements; however, values for HDL are for research purposes only [82].

Inflammatory Markers

C-Reactive Protein (CRP), Interleukin 6 (IL-6), Interleukin 18 (IL-18), and Monocyte Chemoattractant Protein-1 (MCP-1) samples were analyzed in duplicates in 384-well AlphaPlates™ (PerkinElmer®) (Figure 7) according to manufacture low volume protocol. 2 µL of undiluted plasma was used for IL-6, IL-18 and MCP-1 assays, whereas 2 µL of plasma was diluted 101 fold for CRP assays. Absorbance values obtained from the AlphaLISA assays were analyzed using a nonlinear regression 4-parameter logistic equation (sigmoidal dose-response curve with variable slope) and a $1/Y^2$ data weighting (Figure 8). The lowest detectable limit was calculated by averaging background counts and adding that value to 3 times the standard deviation value. All analyses for inflammatory markers were completed using GraphPad Prism software (Version 8.3.0, GraphPad Software, LLC, San Diego, CA). IL-6 values lower than the detection limit (1.3 pg/mL) were assigned a value of 0.01 pg/mL. Replicates with a coefficient of variation greater than 10% were repeated.

Anthropometrics

Body Mass and Stature

Height, pre-dialysis and post dialysis (dry) weights were obtained from the medical record. Clinic staff measured height to the nearest 0.1cm (Tanita Wall Mounted Height Rod, Tanita, USA) and body weight to the nearest 0.1kg after each HD session (Tronix Flush-Mounted In-Floor Scale, Scale-Tronix, USA). BMI was calculated from the measurements of weight and height using Quetelet's Index [BMI (kg/m^2) = weight (kg)/height (m^2)][260].

Muscle Mass

Mid arm circumference (MAC) and triceps skin fold (TSF) thickness was measured following International Society for Advancement of Kinanthropometry (ISAK) procedures [261] by a single Level One trained ISAK Anthropometrist to eliminate inter-observer reliability. In each dialysis clinic, subjects were transported either before or after their dialysis session into an examination room to collect MAC and TSF measurements. Measurements were made on the side of the body without vascular access using the following protocol:

(1) Locate the acromium and the olecranon process; mark these landmarks with an Expo marker. (2) Measure the length between the acromium and the olecranon process and find the midpoint; mark this midpoint with an Expo marker. (3) Measure the arm circumference at this point to the nearest 0.1 cm with a ¼ inch Lufkin flexible steel tape measure (Apex Tool Group, LLC, NC) which is placed gently but firmly around the arm to avoid compression. Record this measurement (Figure 9) (4) Standing perpendicular to the subject, find the furthest point on the triceps, and mark this site with an Expo marker. (5) Measure the TSF using Lange calipers Cambridge Instrument, Cambridge, MA). Holding the skinfold 2.0 cm above the circumference mark, place the tips of the caliper jaws over the complete skinfold. Ensure that the mark remains centered between the tips and that the jaws sit perpendicular to the length of the skinfold. Continue

to hold the skinfold in place and release the caliper handle to exert full tension on the skinfold. Wait 3 seconds for the needle on the caliper dial to settle on an accurate measurement. (6) Repeat MAC and TSF measurement; if the two measurements are more than 1 cm apart, repeat for a third measurement (Figure 9)

MAC and TSF measurements were taken in duplicate using the non-fistula arm, with a third measurement taken when disagreement between the first and second measurements was greater than 10%. Mid arm muscle circumference (MAMC), as a marker of lean muscle mass, was calculated using the formula: MAMC = MAC– (3.14 x TSF thickness) [154, 262].

Muscle Strength

Hand grip strength (HGS) measured by dynamometry is an indicator of muscle strength. The mean of three grip strength trials using the non-fistula arm was measured with a dynamometer using The American Society of Hand Therapists (ASHT) protocol. HGS was measured with subjects seated with their shoulders adducted, their elbows flexed 90°, and their forearms in a neutral position using a Jamar Plus dynamometer (Sammons Preston, Inc., Bolingbrook, IL) with the handle at position 2 [263-265].

Tables and Figures

Table 4: Inflammatory Effect Scores for Dietary Components Used for Calculation of DII

Food parameters	Inflammatory Effect Score*
Carbohydrates (g)	0.097
Cholesterol (mg)	0.11
Calories (kcal)	0.18
Fat (g)	0.298
Total Dietary Fiber (g)	-0.663
MUFA (g)	-0.009
Protein (g)	0.021
PUFA (g)	-0.337
Saturated Fat (g)	0.373
Trans Fatty Acid (g)	0.229
Vitamin B12 (mcg)	0.106
Vitamin B6 (mg)	-0.365
Beta-Carotene (mcg)	-0.584
Folic Acid (mcg)	-0.19
Vitamin B3 (mg)	-0.246
Vitamin B2 (mg)	-0.068
Vitamin B1 (mg)	-0.098
Vitamin A (RE)	-0.401
Vitamin C (mg)	-0.424
Vitamin D (mcg)	-0.446
Vitamin E (mg)	-0.419
Iron (mg)	0.032
Magnesium (mg)	-0.484
Selenium (mcg)	-0.191
Zinc (mg)	-0.313
Omega 3 Fatty Acid (g)	-0.436
Omega 6 Fatty Acid (g)	-0.159
Alcohol (g)	-0.278
Caffeine (mg)	-0.11

Adapted from Shivappa, et, al., 2014 [202].*A negative value indicates anti-inflammatory effect and a positive score indicates pro-inflammatory effect; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid

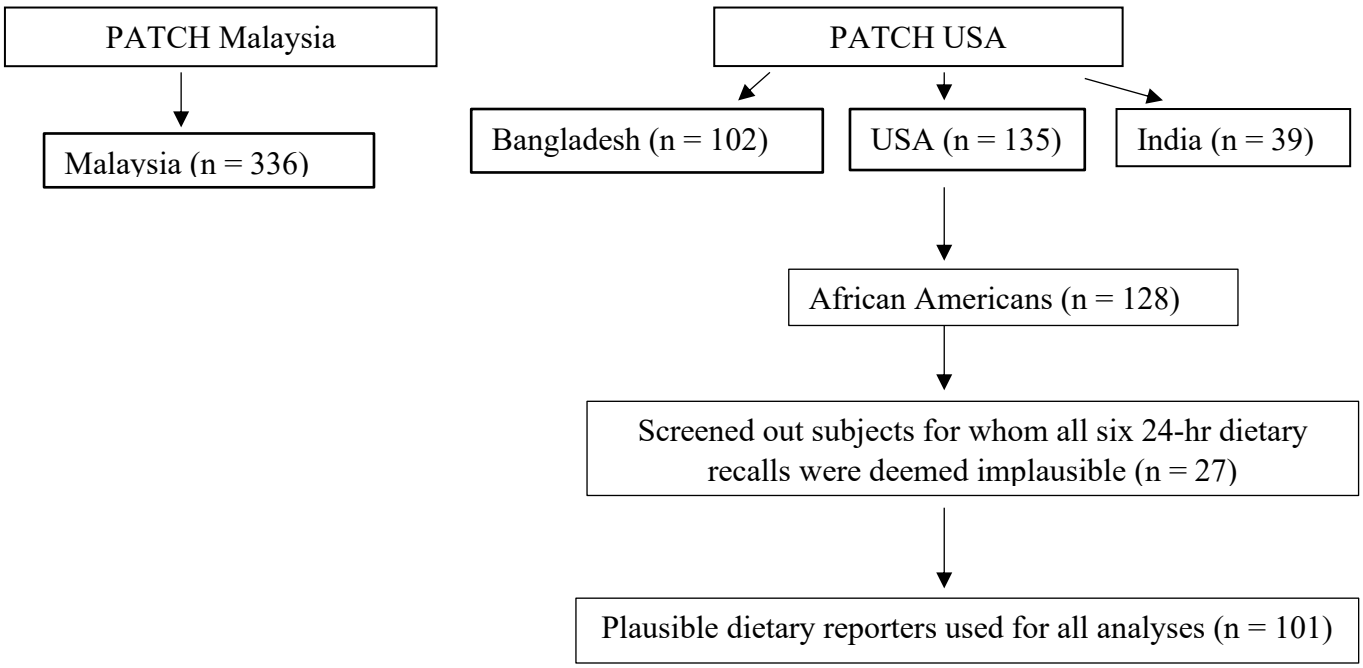


Figure 5: Consort Diagram of PATCH Clinical Trial and Selection of Study Participants

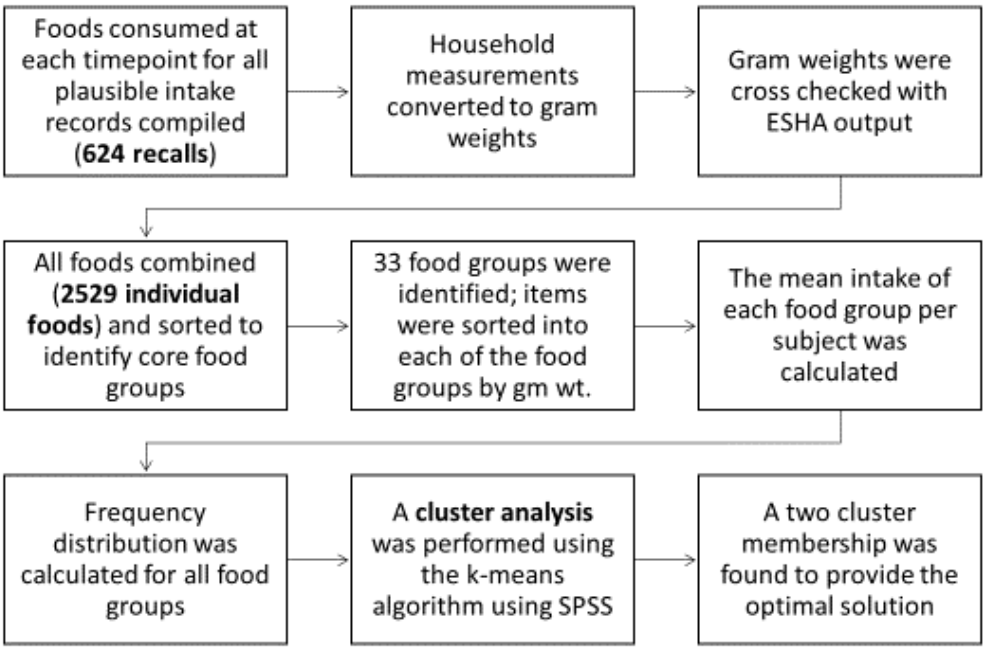


Figure 6: Flow Chart for Dietary Pattern Cluster Analysis Process

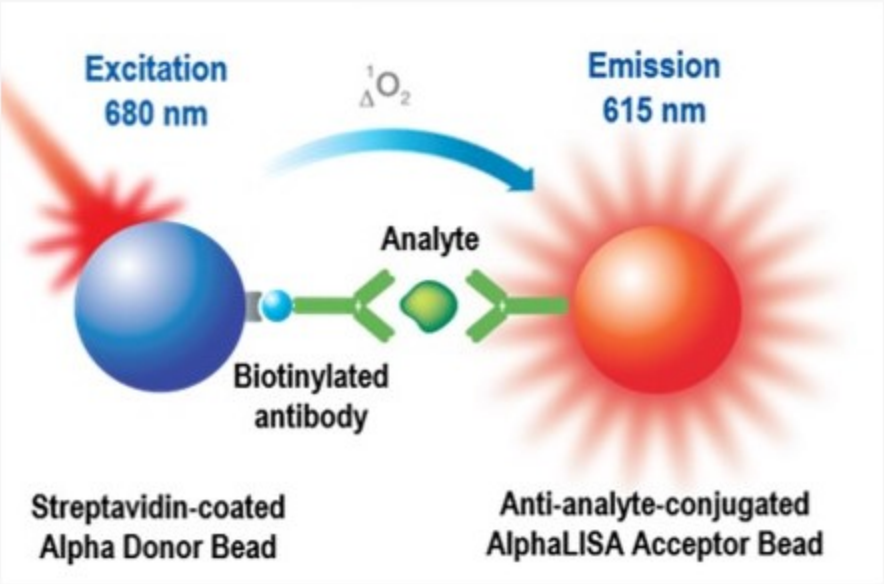


Figure 7: Principles of the AlphaLISA® Assay
(Illustration by: Perkin Elmer®, Inc. 2017)

The AlphaLISA® assay uses a bead-based technology. The energy transferred from one bead to the other produces a luminescent signal.

1) Analyte standard dilutions are prepared according to the manufacture's protocol.
2) In white Optiplate-384 microplate, 2 µL of standard or plasma sample is added to each well using an Eppendorf (K41494G) 8 channel automatic 0.5 – 10 µL pipette.
3) 8 µL of a 2.5X mixture of AlphaLISA Anti-Analyte Acceptor beads (10 µg/mL final) and Biotinylated Antibody Anti-Analyte (1 nM final) are added to each well using an Eppendorf Repeater® M4 pipettor fitted with a Combitip.
4) The plate is covered with a plate seal, spun briefly in a centrifuge, and placed on a shaker plate to incubate for 60 minutes at 23°C.
5) 10 µL of 2X SA-Donor beads (40 µg/mL final) is added to each well.
6) The plate is resealed, spun briefly in a centrifuge, placed on a shaker plate for 3 minutes, and incubated for 30 minutes at 23°C.

7) The plate is read on an EnSpire plate reader.

After the biotinylated antibody and acceptor beads are added, the analyte is captured by the antibody pair to create a sandwich assay. During the first incubation, the biotinylated antibody binds to an epitope on the analyte of interest. The second antibody binds to a different epitope. Once the streptavidin coated donor beads are added, the streptavidin-biotin interaction pulls the complex together, bringing the two beads into close proximity. Donor beads, which contain a photosensitizer (phthalocyanine), converts oxygen to an excited and reactive form of O_2 once illuminated at 680 nm, causing a release of singlet oxygen molecules. The singlet oxygen initiates a cascade of reactions inside the acceptor bead, resulting in a transfer of energy from the singlet oxygen to thioxene derivatives within the acceptor bead, producing light production at 615 nm. The emission wavelength is shorter than the excitation, resulting in less background interference. The higher the concentration of the analyte of interest, the more bead complexes are brought together, which results in a signal intensity proportional to the concentration of the analyte. In the absence of an acceptor bead, singlet oxygen falls to ground state and no signal is produced.

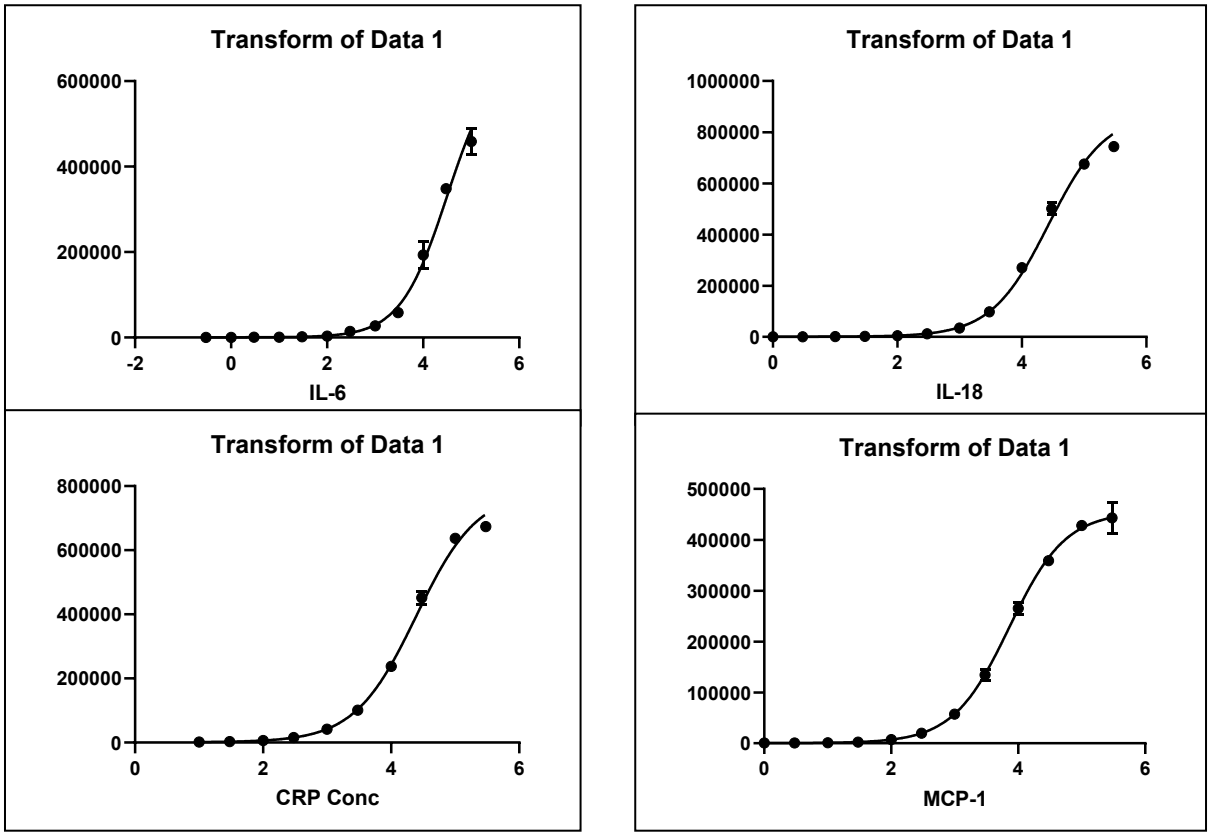
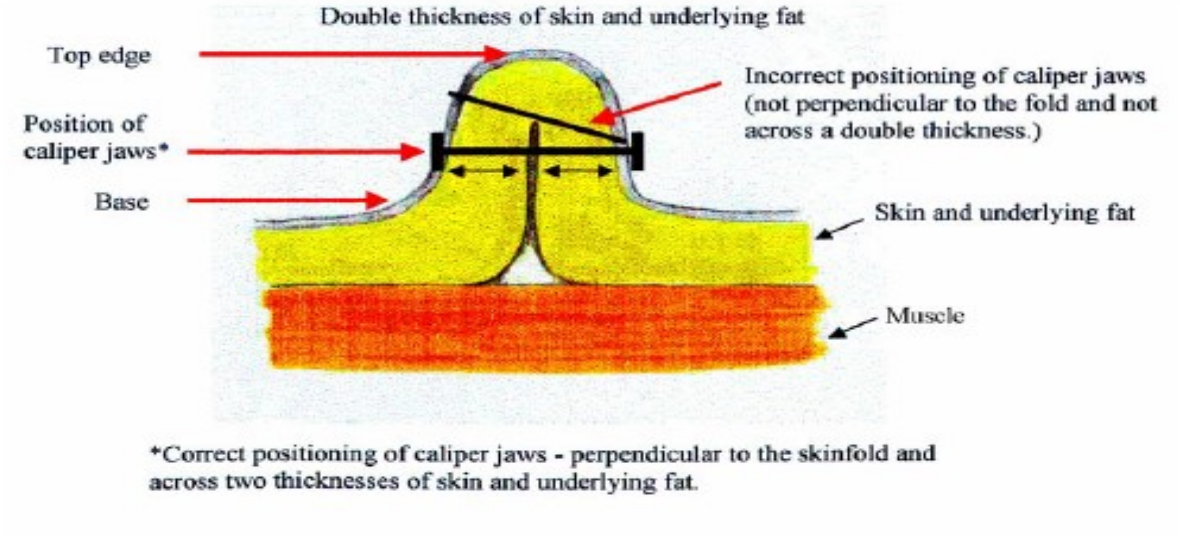
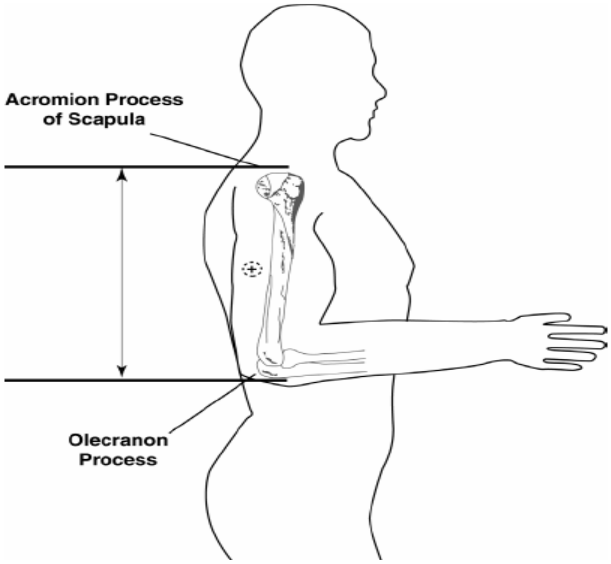


Figure 8: Sigmoidal Dose-Response Curves for Inflammatory Markers (GraphPad Prism)





Position for upper arm length and midpoint

Triceps skin fold measurement

Figure 9: MAC and TSF Measurement (source: GWAS Samoa 2010 – Fieldwork Manual [266])

CHAPTER 3: RESULTS – SPECIFIC AIM ONE: TO CHARACTERIZE THE NUTRITION AND HEALTH STATUS IN A COHORT OF AFRICAN AMERICAN MAINTENANCE HEMODIALYSIS PATIENTS

SUB AIM 1A: To Characterize the Overall Study Population

General Characteristics

The general characteristics of the study participants, displayed in Table 5, did not vary significantly between gender. A total of 101 patients were included in this study, of whom 59% were male; the mean age was 60 years and the average time spent on dialysis was 63 months. One third of the cohort were tobacco users and two-thirds had DM. Women had significantly higher BMI levels compared to men and half of all female subjects had a BMI exceeding 30 kg/m^2 (overweight). The mean Kt/V for the entire cohort was 1.54 ± 0.24. Mean systolic blood pressure did not differ between gender, while mean diastolic readings were significantly lower among females. Approximately half of the study participants were prescribed a renal specific vitamin and one out of five, an antidepressant medication.

Biochemical Characteristics

Biochemical data collected from the HD clinics are shown in Table 6. Measures to assess anemia, hemoglobin, iron, ferritin and transferrin saturation, did not differ significantly between gender. Mean serum ferritin levels for all patients were 757 ± 355 ng/mL; mean hemoglobin levels were 10.8 ± 2.3 g/dL. Serum creatinine levels were significantly higher for males as compared to females, most likely reflective of larger muscle mass. Mean serum potassium was 4.6 ± 0.6 mEq/L, mean serum phosphorus was 5.1 ± 1.2 mg/dL, and mean serum albumin was 3.8 ± 0.3 g/dL; all three of these measures did not differ between genders.

Nutritional Analysis

Macronutrient and micronutrient intakes are presented in Table 7. Although caloric intake and associated micronutrients were significantly higher among males, the macronutrient

distribution did not differ between genders. Approximately 17% of consumed calories were from protein, 40% from fat (12% from saturated fat), and 43% from carbohydrates. For both genders, daily mean intakes for added sugars was 88 grams/day, which is the equivalent to approximately one half cup of sugar (350 calories), which exceeds the American Heart Association's guideline of no more than 36 grams daily. Per the RDA's dietary fiber recommendations for males and females (30 and 21 grams/day, respectively), males met only 43% of the recommended amount and females, 57% [267]. Intakes for sodium, phosphorus, and potassium exceeded recommended guidelines by 76%, 22%, and 82%, respectively, while almost all patients fell below recommended intakes for several micronutrients, including vitamins C, E, K, zinc, and magnesium (Table 8).

Table 5: Baseline Clinical Characteristics of the Study Population

	All (n = 101)	Males (n = 60)	Females (n = 41)	*p* value between groups
Age, y	60 ± 13	59 ± 14	61 ± 12	0.419
Dry weight (kg)	84 ± 19	86 ± 22	82 ± 18	**< 0.001**
Height (cm)	172 ± 11	178 ± 8	165 ± 7	0.367
BMI, kg/m^2	28.4 ± 6.6	27.1 ± 6.3	30.3 ± 6.6	**0.016**
Obese (BMI > 30), %	36 (36)	15 (25)	21 (51)	**0.036**
Vintage (months)	63 ± 63	66 ± 67	59 ± 56	0.543
IDWG (kg)	2.7 ± 1.4	2.8 ± 1.5	2.4 ± 1.3	0.129
UFR (mL/kg/hr)	6.6 ± 4.1	7.0 ± 4.4	5.9 ± 3.6	0.172
DM, n (%)	58 (57)	34 (57)	24 (59)	0.852
Tobacco Use, n (%)	29 (29)	13 (22)	16 (39)	0.058
Vascular Access				
Arteriovenous fistula, n (%)	59 (58)	33 (55)	26 (63)	0.642
Arteriovenous graft, n (%)	27 (27)	18 (30)	9 (22)	
Catheter, n (%)	15 (15)	9 (15)	6 (15)	
Blood Pressure, mmHg (post-sitting)				
[1]Systolic	140 ± 23	138 ± 23	144 ± 23	0.240
[1]Diastolic	79 ± 17	82 ± 20	74 ± 9	**0.023**
Kt/V	1.54 ± 0.24	1.53 ± 0.21	1.56 ± 0.27	0.559
Antidepressant use, %	17 (17)	8 (13)	9 (22)	0.256
Renal vitamin* use, %	56 (55)	34 (57)	22 (54)	0.765

Values are expressed as means ± SDs, or percentages. Statistics: 2-sample t test, or Pearson chi-square test. BMI: Body Mass Index; IDWG: Interdialytic Weight Gain; UFR: Ultrafiltration Rate; DM, diabetes mellitus; Kt/V is a number used to quantify hemodialysis (K, dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea, approximately equal to patient's total body water) *Renal vitamins included Nephrocaps, Renal Caps, and Nephrovite brands. [1]BP (n = 88)

Table 6: Baseline Clinic Reported Biochemical Characteristics of the Study Population

	All (n = 97)	Males (n = 57)	Females (n = 40)	*p* value between groups
Serum Potassium (mEq/L)	4.6 ± 0.6	4.6 ± 0.6	4.6 ± 0.6	0.725
Serum Phosphorus (mg/dL)	5.1 ± 1.2	5.3 ± 1.3	4.9 ± 1.0	0.102
Serum Albumin (g/dL)	3.8 ± 0.3	3.8 ± 0.4	3.8 ± 0.3	0.757
Corrected Calcium (mg/dL)	9.3 ± 0.7	9.3 ± 0.8	9.3 ± 0.5	0.662
Serum Creatinine (mg/dL)	9.3 ± 2.7	9.9 ± 2.8	8.4 ± 2.4	**0.008**
Serum Hemoglobin (g/dL)	10.8 ± 2.3	10.7 ± 1.4	11.0 ± 3.2	0.650
Serum Iron (μg/dL)	74 ± 39	65 ± 23	85 ± 53	0.060
Serum Ferritin (ng/mL)	757 ± 355	718 ± 344	812 ± 369	0.212
TSAT (%)	30 (11)	31 (9)	31 (13)	0.572

Values are expressed as means ± SDs, or percentages. Statistics: 2-sample t test, or Pearson chi-square test. TSAT: Transferrin Saturation

Table 7: Nutrient Intake of the Study Population

	All (n = 101)	Males (n = 60)	Females (n = 41)	*p* value between groups
Calories (kcals)	2033 ± 417	2183 ± 417	1815 ± 311	**< 0.001**
Protein (g)	86 ± 26	94 ± 28	75 ±18	**< 0.001**
% kcals from protein	17 ± 4	17 ± 5	17 ± 4	0.376
Fat (g)	91 ± 25	96 ± 23	83 ± 24	**0.007**
% kcals from fat	40 ± 7	40 ± 7	41 ± 7	0.463
Saturated fat (g)	28 ± 9	30 ± 9	26 ± 8	**0.008**
% kcals from SFA	12 ± 3	12 ± 3	13 ± 3	0.722
Cholesterol (mg)	417 ± 182	431 ± 191	396 ± 169	0.331
Carbohydrate (g)	219 ± 65	236 ± 72	193 ± 44	**< 0.001**
% kcals from carbohydrate	43 ± 8	43 ± 8	43 ± 8	0.881
Fiber (g)	12 ± 4	13 ± 4	12 ± 5	0.122
Sugar (g)	88 ± 45	93 ± 49	80 ± 38	0.122
Phosphorus (mg)	837 ± 303	924 ± 325	709 ± 215	**< 0.001**
Iron (mg)	11 ± 4	12 ± 4	10 ± 5	0.076
Magnesium (mg)	149 ± 64	168 ± 69	120 ± 43	**< 0.001**
Sodium (mg)	3004 ± 960	3190 ± 1021	2731 ± 798	**0.013**
Potassium (mg)	1503 ± 583	1653 ± 599	1283 ± 487	**0.001**
Zinc (mg)	8.5 ± 4.1	9.4 ± 4.1	7.1 ± 3.8	**0.005**
Vitamin C (mg)	57 ± 46	63 ± 47	49 ± 43	0.117
Calcium (mg)	436 ± 154	165 ± 21	125 ± 20	**0.011**
Chromium (mcg)	4.4 ± 6.9	5.0 ± 7.8	3.4 ± 5.0	0.244
Selenium (mg)	89 ± 38	94 ± 42	81 ± 29	0.074
Folate (mcg)	224 ± 108	239 ± 120	204 ± 84	0.090
Cholesterol (mg)	417 ± 182	431 ± 191	396 ± 169	0.331
Vitamin A (IU)	3563 ± 3290	3385 ± 3155	3823 ± 3502	0.522
Vitamin D (IU)	90 ± 74	94 ± 87	85 ± 49	0.528
Vitamin E (mg)	4.2 ± 3.1	4.6 ± 3.5	3.7 ± 2.4	0.148
Vitamin K (mcg)	56 ± 80	58 ± 81	53 ± 81	0.791

Values are expressed as means ± SDs, or percentages. Statistics: 2-sample t test, or Pearson chi-square test. kcals: kilocalories

Table 8: Percentage of Patients Outside the Recommended Intake Limits of Micronutrients

	All (n = 101)	Nutrient recommendations for HD [154]	Patients (%) outside the recommended intake limits
Sodium, mg/d	2858 [2345 – 3581]	750 – 2000	90
Phosphorus, mg/d	791 [621 – 988]	≤ 800 – 1000	22
Potassium, mg/d	1457 [1096 – 1770]	800 – 1000	82
Calcium, mg/d	421 [320 – 497]	≤ 1000	none
Magnesium, mg/d	135 [109 – 175]	200 – 300	97
Selenium, mg/d	87 [62 – 105]	55*	18
Zinc, mg/d	7.6 [5.9 – 10.6]	15	90
Vitamin A, IU/d	2149 [1347 – 4862]	700-900	6
Vitamin C, mg/d	48 [24 – 86]	75 – 90	71
Vitamin E, mg/d	3.3 [2.3 – 5.4]	15	97
Vitamin K, mcg/d	30 [13 – 60]	90 – 120	87

Values are expressed as median [interquartile range (IQR)]. No guidelines specific to HD population available; Recommended Dietary Allowance(RDA)/Dietary Guidelines for Americans DGA used[267, 268]

SUB AIM 1B: To Assess Protein Energy Wasting (PEW), Dyslipidemia, and Inflammation in the Study Population

Protein Energy Wasting (PEW)

Patients were identified as having PEW if three of the four criteria were met: (1) albumin < 3.8mg/dL, (2) BMI < 23 kg/m^2, (3) reduced mid-arm muscle circumference area (reduction > 10% in relation to 50th percentile of reference population), and (4) either DEI < 25 kcals/kg or DPI < 0.8 grams/kg recorded for one of the 24-hr dietary recalls. Figure 10 shows a frequency distribution of PEW prevalence for each of four criteria. 60% of patients had a low DEI or DPI, 41% had a low albumin level, 23% had a low BMI, and 15% had a low MAMC. Only five patients (5%) were identified as having three of the four diagnostic criteria for PEW.

Using the EWGSOP2 sarcopenia cut-off points for low grip strength (27 kg and 16 kg for men and women, respectively), 27% of males and 19% of females met the criteria for probable sarcopenia (Table 9). Further analyses were conducted to examine the differences in biomarkers, macronutrient, and micronutrient intakes as well as self-reported outcome measures. Patients meeting the criteria for probable sarcopenia tended to be older (64 ± 13 vs. 59 ± 12 years) and have a longer dialysis vintage (98 ± 105 vs 60 ± 52 months); however, these differences were not significant. No significant differences in inflammatory markers were found between sarcopenic and non-sarcopenic patients, with the exception of CRP (6.9 ± 2.1 vs 4.3 ± 2.8 mg/L, p = 0.003), which was significantly higher for those patients with probable sarcopenia.

Dyslipidemia and Inflammation

The biochemical characteristics of the study participants are presented in Table 10. One subject with hypertriglyceridemia (plasma TAG 943 mg/dL) was excluded from all subsequent analyses. In comparison to males, female patients presented with significantly higher TC, HDL-

C, and large and intermediate HDL, and large LDL subfractions. Males were about twice as likely (RR = 1.95) to have an atherogenic Pattern B phenotype than females.

Using a threshold of non-HDL cholesterol > 100 mg/dL to identify patients with dyslipidemia [269], 44% of the cohort were classified as dyslipidemic. For the entire cohort, both large and intermediate HDL and LDL subfractions were more prevalent in contrast to small HDL and LDL subfractions.

Using a TG/HDL-C ratio of 3.8, as derived from the Adult Treatment Panel target recommendations of TG > 150 mg/dl and HDL-C < 40 mg/dl, only 15% of patients were categorized as having a TG/HDL ratio of > 3.8 [270]. Results from a t-test comparing inflammatory markers for those patients with a TG/HDL-C ratio > 3.8 vs < 3.8, respectively showed the following difference in means: MCP-1 (123 ± 85 vs. 148 ± 117, NS), IL-6 (1.5 ± 3.1 vs. 14.0 ± 50.6, p = 0.028), and IL-18 (219 ± 130 vs. 277 ± 158, NS), thus patients with a TG/HDL-C ratio > 3.8 tended towards lower levels of inflammatory markers.

Correlations between malnutrition and inflammation indicators are presented on Table 11. BMI was positively correlated with both TSF, $r(45) = 0.78$, $p < 0.001$ and MAMC, $r(45) = 0.76$, $p < 0.001$. There was a significant, moderately positive correlation between HGS and serum creatinine, $r(45) = 0.43$, $p = 0.003$. MAMC and HGS were positively correlated, but the relationship was not significant. The only inflammatory marker found to be associated with anthropometric measures was CRP, which had a weak, positive association with BMI, $r(97) = 0.25$, $p = 0.013$.

Significant associations were found among the measured cytokines illustrated on Figure 11. IL-18 was moderately positively associated with its downstream products, MCP-1, $r(94) = 0.46$, $p < 0.001$ and IL-6, $r(97) = 0.48$, $p < 0.001$. However, no significant associations were found

between the cytokines and CRP. Additionally, a negative weak association was found between CRP and albumin, $r(93) = -0.28$, $p = 0.005$.

Table 9: Baseline Anthropometric Measures of the Study Population

	All (n = 47)	Males (n = 26)	Females (n = 21)	*p* value between groups
Hand Grip Strength (kg)	25.8 ± 10.0	30.8 ± 10.7	19.7 ± 3.6	**< 0.001**
TSF (mm)	16.6 ± 9.9	15.1 ± 10.2	18.5 ± 9.3	0.245
MAMC (cm)	27.5 ± 4.2	27.3 ± 3.5	27.8 ± 4.9	0.718
Low Grip Strength	11 (23)	7 (27)	4 (19)	0.526

Values are expressed as means ± SDs, or percentages. Statistics: 2-sample t test, or Pearson chi-square test; BMI: Body Mass Index; TSF: triceps skin fold; MAMC: mid-arm muscle circumference.

Table 10: Baseline Lipid and Inflammatory Characteristics of the Study Population

	[1]All (n = 100)	Males (n = 59)	Females (n = 41)	*p* value between groups
CRP (mg/L)	6.1 ± 4.0	6.4 ± 4.6	5.6 ± 2.9	0.273
IL-6 (pg/mL)	12.1 ± 46.7	16.9 ± 59.5	5.3 ± 13.1	0.157
IL-18 (pg/mL)	268 ± 155	292 ± 179	230 ± 99	**0.003**
MCP-1 (pg/mL)	144 ± 112	168 ± 137	109 ± 45	**0.003**
Total Cholesterol (mg/dL)	151 ± 44	141 ± 41	165 ± 46	**0.007**
Triglycerides (mg/dL)	96 ± 52	91 ± 50	104 ± 56	0.237
LDL-C (mg/dL)	80 ± 40	75 ± 35	86 ± 47	0.204
HDL-C (mg/dL)	52 ± 19	47 ± 17	58 ± 21	**0.007**
non-HDL-C > 100 mg/dl (n, %)	44 (44)	22 (37)	22 (54)	0.105
TG/HDL-C > 3.8	15 (15)	7 (12)	8 (20)	0.292
Large HDL (mg/dL)	22.8 ±16.2	19.5 ± 13.1	27.5 ± 19.1	**0.023**
Intermediate HDL (mg/dL)	22.8 ± 5.8	21.6 ± 5.6	24.6 ± 5.8	**0.012**
Small HDL (mg/dL)	6.1 ± 3.3	6.0 ±3.1	6.2 ± 3.5	0.764
Large LDL(mg/dL)	21.9 ± 9.7	19.5 ± 8.6	25.5 ± 10.3	**0.003**
Intermediate LDL (mg/dL)	12.7 ± 8.1	11.8 ± 6.9	14.0 ± 9.6	0.230
Small LDL (mg/dL)	3.9 ± 5.5	4.3 ± 5.0	3.5 ± 6.2	0.506
Mean LDL Size (Å)	269 ± 4	269 ± 5	270 ± 4	**0.046**
LDL Pattern A, n (%)	62 (62)	31 (53)	31 (80)	**0.024**
LDL Pattern B, n (%)	16 (16)	12 (20)	4 (10)	

Values are expressed as means ± SDs, or percentages. Statistics: 2-sample t test, or Pearson chi-square test. [1]One subject with hypertriglyceridemia (plasma TAG 943 mg/dL) excluded from table. CRP: C-reactive protein; IL-6: Interleukin 6; IL-18: Interleukin 18; MCP-1: Monocyte Chemoattractant Protein-1; HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; Å: angstrom.

Table 11: Correlation Matrix for Anthropometric and Inflammation Indicators

Variable	CRP	MCP-1	IL-18	IL-6	Alb	Creat	TSF	MAMC	HGS	BMI
MCP-1	0.12	-								
IL-18	-0.06	0.46***	-							
IL-6	0.05	0.48***	0.50***	-						
Alb	-0.28**	-0.08	0.04	0.10	-					
Creat	-0.10	0.19	0.26**	0.28**	-0.20*	-				
TSF	0.24	-0.06	0.07	0.13	-0.20	0.06	-			
MAMC	0.09	0.00	-0.19	0.08	-0.25	0.21	0.45***	-		
HGS	-0.26	0.28	0.06	-0.07	-0.14	0.43***	0.56	0.27	-	
BMI	0.25**	-0.18	-0.10	-0.06	-0.01	-0.05	0.78***	0.76***	0.03	-
DII	-0.12	-0.04	-0.06	-0.19	0.20	-0.09	0.01	-0.07	-0.12	-0.11

*P < 0.05; **P < 0.01; ***P < 0.001

CRP: C-reactive protein; MCP-1: Monocyte Chemoattractant Protein-1; IL-18: Interleukin 18; IL-6: Interleukin 6; Alb: albumin; Creat: creatinine; TSF: Triceps Skin Fold; MAMC: Mid arm muscle circumference; HGS: Hand Grip Strength; BMI: Body Mass Index; DII: Dietary inflammatory index

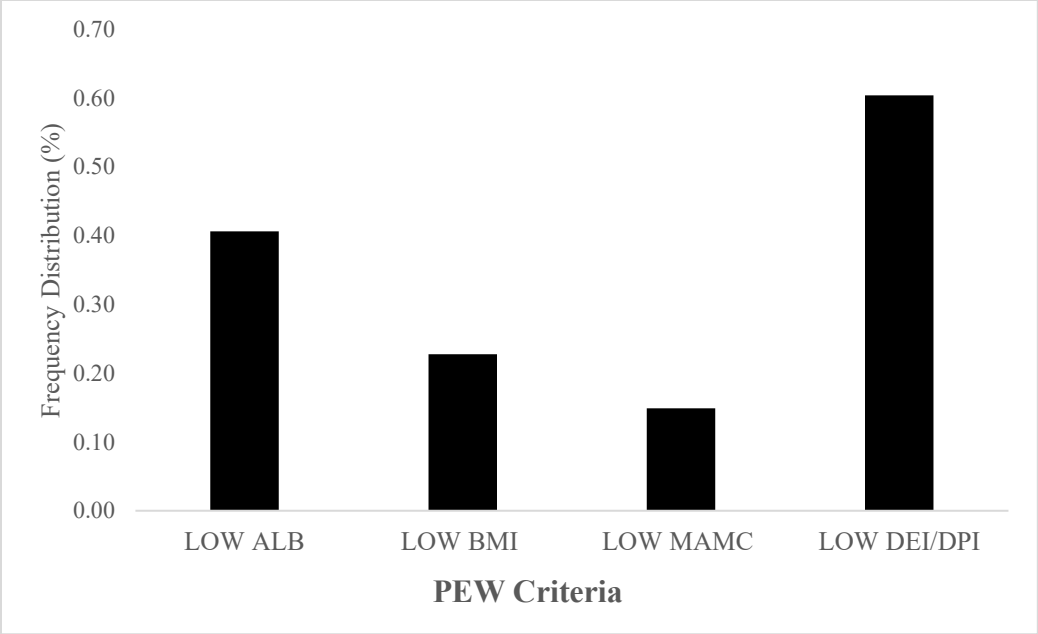


Figure 10: Frequency Distribution of PEW Prevalence for Each of Four Criteria
ALB: albumin (n= 96); BMI: Body Mass Index (n = 101); MAMC: mid arm muscle circumference (n = 47); DEI: dietary energy intake and DPI: dietary protein intake (DPI) (n = 101)

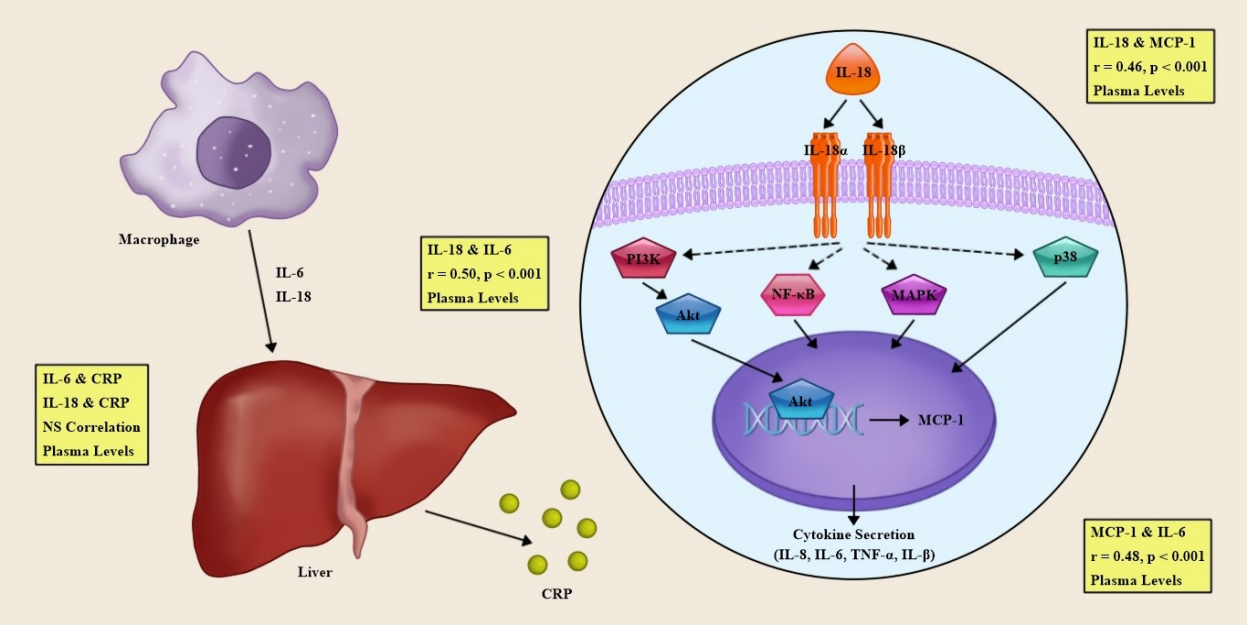


Figure 11: Plasma Cytokine Correlations for IL-18 and MCP-1, MCP-1 and IL-6, and IL-6 and CRP

SUB AIM 1C: To Evaluate Phosphorus to Protein Ratio and Dietary Inflammatory Index From the Derived Nutrition Information

Associations with Egg Intake

For those participants who reported consuming egg, bivariate (Pearson) correlations were conducted to examine the relationship between percent of total energy intake (% TE) contribution from egg and outcome measures. Higher % TE from egg was negatively associated with HGS, $r(32) = -0.37$, $p = 0.034$ and positively associated with PTH, $r(84) = 0.33$, $p = 0.002$.

A multivariate analysis (Table 12 and Table 13) was conducted to examine the differences in serum chemistry and BMI between those participants who reported any egg consumption against those who did not report egg consumption. To reduce confounding, a separate analysis was conducted for each gender and results were adjusted for age. No differences were observed for BMI, serum lipids, phosphorus, albumin, and PTH for both genders, with the exception of TC in men; egg consumers had a significantly lower TC (132 ± 37 mg/dL) as compared to non-consumers (160 ± 43 mg/dL).

The mean DII score was 3.1 ± 1.1 (min, -0.54; max, 5.83). A gender stratified analysis was conducted to examine differences in inflammatory markers, serum albumin and creatinine, and dietary intake according to DII (Table 14). Scores ranging from -0.54 to 3.26 were classified as "lower DII scores" while scores ranging from 3.27 to 5.83 were classified as "higher DII scores." No differences were found between those with lower and higher DII scores for inflammatory markers, serum albumin and serum creatinine for both genders. Significant differences in PUFA intake was found between lower and higher DII score groups. For both males and females, consuming fewer calories from PUFA was significantly associated with higher DII scores. Males in the higher DII group consumed significantly less α-linolenic (ALA) and linoleic acid (LA) than

those in the lower DII group. Lower intakes of both ALA and LA were also found for females who consumed more inflammatory diets.

It is worth noting that both males and females in the entire cohort fell short of the Recommended Dietary Allowance (RDA) for α-linolenic acid, which is 1.6 and 1.1 grams/day, respectively, for males and females ages 51 to 70. Only subjects who fell in the lower DII score groups met the RDA for linoleic acid (14 and 11 grams/day, respectively for males and females for ages 51 to 70) [267].

Phosphorus to Protein (P/Pro) Ratio

Comparisons between those subjects consuming "favorable" p/pro ratio of less than 10 mg/g and those consuming "unfavorable" ratios of greater than 10 mg/g were compared (Table 14). A cutoff value of 10 mg/g as the upper end of favorable was used based on current recommendations per Noori, et al. [156]. No significant differences were found in serum chemistry, namely serum phosphorus and PTH. No differences were found in serum lipids and inflammatory markers. Significantly higher intakes of percent calories from MUFAs and PUFAs were observed in the "unfavorable" p/pro group. Gram intake of eggs was higher in the unfavorable p/pro group, but this difference was not significant.

Table 12: Multivariate Analysis of Egg Non-Consumers Versus Consumers for Men

	Did not consume eggs (n = 17)	Consumed eggs (n = 38)	95 % CI		*p* value
			Lower limit	Upper limit	
BMI, kg/m^2	26.1 ± 4.6	27.4 ± 6.8	-4.96	2.42	0.493
Total Cholesterol (mg/dL)	160 ± 43	132 ± 37	3.35	49.16	**0.026**
Triglycerides (mg/dL)	109 ± 61	84 ± 43	-6.04	51.55	0.119
LDL-C (mg/dL)	89 ± 37	70 ± 34	-1.50	40.12	0.068
HDL-C (mg/dL)	49 ± 24	46 ± 13	-7.31	12.09	0.623
Serum Phosphorus (mg/dL)	5.3 ± 1.2	5.3 ± 1.4	-0.88	0.64	0.749
Serum Albumin (g/dL)	3.9 ± 0.4	3.8 ± 0.3	-0.19	0.22	0.901
PTH	466 ± 255	700 ± 715	-617.76	109.96	0.167

Adjusted for age; One subject with hypertriglyceridemia (plasma TAG 943 mg/dL) excluded from table.

Table 13: Multivariate Analysis of Egg Non-Consumers Versus Consumers for Women

	Did not consume eggs (n = 6)	Consumed eggs (n = 34)	95 % CI		*p* value
			Lower limit	Upper limit	
BMI, kg/m^2	34.3 ± 5.2	29.6 ± 6.7	-1.94	11.60	0.157
Total Cholesterol (mg/dL)	146 ± 42	166 ± 44	-66.97	24.68	0.356
Triglycerides (mg/dL)	103 ± 60	103 ± 56	-57.25	61.03	0.949
LDL-C (mg/dL)	75 ± 44	85 ± 45	-60.75	32.28	0.539
HDL-C (mg/dL)	51 ± 20	60 ± 21	-29.16	14.58	0.504
Serum Phosphorus (mg/dL)	5.4 ± 1.3	4.8 ± 1.0	-0.64	1.45	0.438
Serum Albumin (g/dL)	3.7 ± 0.1	3.8 ± 0.3	-0.53	0.06	0.108
PTH	460 ± 429	705 ± 612	-809.04	419.37	0.524

Adjusted for age

Table 14: Characteristics of the Patients According to Lower and Higher Dietary Inflammatory Intake Scores (DII)

Characteristics	Males			Females		
	Lower DII scores (n = 34)	Higher DII scores (n = 26)	p value	Lower DII scores (n = 16)	Higher DII scores (n = 25)	*p* value
DII	2.2 ± 0.9	4.0 ± 0.6	**< 0.001**	2.5 ± 0.5	3.9 ± 0.4	**< 0.001**
CRP (mg/L)	6.8 ± 5.2	5.9 ± 3.6	0.471	4.7 ± 2.5	6.2 ± 3.1	0.106
IL-6 (pg/mL)	20.6 ± 69.7	11.5 ± 42.6	0.541	6.6 ± 19.3	4.4 ± 6.8	0.671
IL-18 (pg/mL)	293 ± 185	288 ± 172	0.925	218 ± 90	239 ± 106	0.520
MCP-1 (pg/mL)	156 ± 64	181 ± 193	0.538	114 ± 52	106 ± 40	0.597
Serum Alb (g/dL)	3.8 ± 0.4	3.9 ± 0.3	0.591	3.7 ± 0.4	3.9 ± 0.2	0.177
Serum Cr (mg/dL)	9.9 ± 3.0	9.6 ± 2.7	0.691	7.9 ± 1.8	8.7 ± 2.7	0.265
% kcal from fat	39 ± 7	40 ± 6	0.595	38 ± 8	42 ± 6	**0.050**
% kcal from SFA	12 ± 3	13 ± 2	**0.027**	12 ± 3	13 ± 2	0.492
% kcal from PUFA	7 ± 3	5 ± 3	**0.002**	7 ± 3	5 ± 2	**0.033**
% kcal from MUFA	13 ± 4	9 ± 5	**0.005**	11 ± 4	11 ± 4	0.539
ALA	1.0 ± 0.5	0.7 ± 0.4	**0.021**	0.8 ± 0.4	0.6 ± 0.2	0.072
LA	13.8 ± 9.3	8.4 ± 4.7	**0.005**	11.5 ± 7.5	7.5 ± 3.0	0.056

DII: Dietary inflammatory index; Lower scores: -0.54 to 3.26 and higher scores: 3.27 to 5.83; CRP: C-reactive protein; IL-6: Interleukin 6; IL-18: Interleukin 18; MCP-1: Monocyte Chemoattractant Protein-1; Alb: albumin; Cr: creatinine; kcal: kilocalories; SFA: Saturated fatty acids: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids; ALA: Alpha-linolenic acid; LA: Linoleic acid

Table 15: Differences Between "Favorable" and "Unfavorable" P/Pro Ratios

	P/Pro < 10 mg/g (n=55)	P/Pro > 10 mg/g (n=46)	*p* value between groups
Serum Chemistry			
Potassium (mEq/L)	4.6 ± 0.7	4.7 ± 0.5	0.670
Phosphorus (mg/dL)	5.0 ± 1.3	5.2 ± 1.1	0.649
Albumin (g/dL)	3.8 ± 0.4	3.8 ± 0.3	0.688
Creatinine (mg/dL)	9.3 ± 3.0	9.2 ± 2.5	0.853
PTH	580 ± 493	706 ± 105	0.316
BMI (kg/m^2)	29.3 ± 7.1	27.3 ± 5.8	0.125
IDWG (kg)	2.7 ± 1.3	2.7 ± 1.6	0.921
UFR (mL/kg/hr)	7.2 ± 4.3	5.8 ± 3.8	0.095
Dietary Nutrients			
p/pro ratio (mg/g)	8.1 ± 1.7	12.0 ± 2.2	**< 0.001**
grams pro/kg BW	26 ± 6	25 ± 5	0.525
% kcals from carbohydrate	43 ± 7	43 ± 9	0.639
% kcals from protein	18 ± 4	17 ± 4	0.424
% kcals from fat	40 ± 6	40 ± 7	0.696
% kcals from carbohydrate	43 ± 7	43 ± 9	0.639
% kcals from SFA	13 ± 3	12 ± 3	0.746
% kcals from MUFA	10 ± 3	13 ± 4	**< 0.001**
% kcals from PUFA	5 ± 2	7 ± 3	**< 0.001**
Egg intake (g)	44 ± 42	62 ± 49	0.059

Values are expressed as means ± SDs. Statistics: 2-sample t test. "favorable" p/pro group: < 10 mg/g; "unfavorable" p/pro group: > 10 mg/g PTH: parathyroid hormone; BMI: body mass index; IDWG: interdialytic weight gain; UFR: ultrafiltration rate; BW: body weight SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids.

CHAPTER 4: RESULTS – SPECIFIC AIM TWO: TO EVALUATE THE ASSOCIATION OF CLUSTER ANALYSIS DERIVED DIETARY PATTERNS WITH HEALTH OUTCOMES IN A COHORT OF AFRICAN AMERICAN MAINTENANCE HEMODIALYSIS PATIENTS

Clusters Identified for Dietary Patterns

Two major dietary patterns were identified: (Cluster 1) a high "sugar sweetened beverage" pattern (hiSSB) and (Cluster 2) a low "sugar sweetened beverage" pattern (loSSB). As illustrated in Table 16, the hiSSB dietary pattern was characterized by higher energy contributions from calorically sweetened soft and juice drinks ($p < 0.001$) and poultry ($p < 0.05$), whereas the greatest energy contributors to the loSSB group was unprocessed red meat ($p < 0.05$), fish and shellfish, ($p < 0.05$), and custard style desserts such as puddings, ice cream, and cheesecake ($p < 0.05$). A total of 54 patients were classified in the loSSB pattern and 47 patients in the hiSSB pattern.

Characteristics of Patients According to Dietary Cluster

Baseline characteristics of the subjects were compared according to diet clusters. One subject with hypertriglyceridemia (plasma TAG 943 mg/dL) was considered an influential outlier and was therefore excluded the analyses to minimize statistical bias. Clinical parameters did not differ significantly between the two diet clusters. Compared to patients in the loSSB group, those in the hiSSB group had a significantly higher BMI and were more likely prescribed an antidepressant. Both total HDL cholesterol as well as large HDL subfractions were significantly lower in the hiSSB group as compared to the loSSB group. Patients in the hiSSB group were 2.4 times more likely to present a pattern B phenotype, which is distinguished by smaller and denser LDL subfractions. Although the association was not significant, the hiSSB dietary pattern tended towards higher inflammatory markers for CRP, IL-18, and MCP-1 (Table 17).

Nutrient Intake According to Dietary Cluster

The nutrient intake of the subjects according to their diet cluster is illustrated in Table 18. The two dietary clusters differed significantly in macronutrient distribution, with a larger proportion of energy intake from fat and protein in the loSSB group and from carbohydrate in the hiSSB group. Macronutrient intakes for cholesterol were significantly higher in the loSSB group and intakes for total energy and sugar were significantly higher in the hiSSB group. Micronutrient intakes differed significantly between groups for chromium (Cr), selenium (Se), vitamin C, and zinc (Zn). Intakes for Cr, Se and Zn were lower in the hiSSB group as compared to the loSSB group.

Based on the RDA, both clusters exceeded the Acceptable Macronutrient Distribution Ranges (AMDR) for fat [267] and the Dietary Guidelines for Americans (DGA) recommendations for both sodium and sugars [268]. Intakes for fiber, magnesium (Mg), Zn, vitamins C and E, Cr, and folic acid fell below RDA guidelines for both groups [267]. USDA My Plate recommendations fell below recommended minimum serving amounts for grains, vegetables, fruits, and dairy. The hiSSB group exceeded the minimum recommended servings for protein by 132% and the loSSB cluster, by 162% [271].

KDQOL Among MHD Patients According to Diet Clusters Among MHD Patients

Figure 12 illustrates the difference in KDQOL scores according to diet clusters. Compared to those in the loSSB dietary pattern cluster, patients in the hiSSB cluster scored lower baseline values on all five KDQOL domains and significantly lower on the S12 mental composite domain ($p < 0.026$). To compare KDQOL scores across each domain for additional variables, a univariate analysis was conducted (Table 19). The burden composite score was positively associated with

vintage; symptoms and effects scores were positively associated with age, and the physical component summary score was negatively associated with vintage.

Table 16: Percentage of Energy Contribution of Food Groups

Food Groups	Pattern 1 (hiSSB) Mean (SD) %TE food	Pattern 2 (loSSB) Mean (SD) %TE food	*p* value
Sugar sweetened beverages	27.97 ± 9.27	9.45 ± 5.65	**< 0.001**
Unprocessed red meat	0.95 ± 1.49	2.17 ± 3.49	**0.022**
Poultry	4.67 ± 5.99	2.51 ± 2.47	**0.024**
Fish and shellfish	0.49 ± 0.93	1.42 ± 2.87	**0.028**
Puddings, ice cream, cheesecake	0.24 ± 0.78	0.76 ± 1.70	**0.049**
Processed and cured meats (bacon, sausage, hot dogs)	2.67 ± 2.47	3.62 ± 3.39	0.106
Dairy, low-fat and 2%	1.75 ± 4.61	0.59 ± 2.30	0.122
Egg and egg dishes	2.43 ± 2.60	3.29 ± 3.08	0.132
Vegetables, canned, fresh and frozen	3.25 ± 4.20	4.45 ± 4.11	0.151
Fast foods, frozen and convenience entrees	4.46 ± 6.67	2.92 ± 4.87	0.194
Pizza, pasta and lasagna	2.77 ± 4.95	4.25 ± 6.58	0.200
Butter, margarine, animal fats	0.25 ± 0.41	0.41± 0.95	0.256
Potatoes, mashed and salad	0.87 ± 2.16	1.39 ± 2.55	0.270
Beans and legumes	0.43 ± 1.25	0.75 ± 1.92	0.315
Potatoes, fried and hash browns	1.39 ± 2.26	0.96 ± 2.18	0.330
Fruit, canned, fresh and dried	2.02 ± 4.61	1.28 ± 2.53	0.335
Oils (vegetable, olive, canola)	0.03 ± 0.09	0.05 ± 0.20	0.398
Crackers, chips and popcorn	2.12 ± 4.80	1.60 ± 2.57	0.509
Candy	0.47 ± 1.11	0.34 ± 1.01	0.542
Sauce and condiments, savory	0.83 ± 1.50	0.69 ± 0.92	0.597
Nuts and seeds and nut butters	0.24 ± 0.84	0.17 ± 0.86	0.665
Dairy, full-fat and creamer	1.00 ± 3.00	0.75 ± 3.18	0.691
Cakes, cookies, pie, donuts, and rich dough	1.71 ± 2.34	1.78 ± 2.70	0.885
Grains	6.38 ± 8.63	6.62 ± 8.26	0.888
Pork	0.71 ± 2.22	0.76 ± 1.65	0.889
Sauces and condiments, sweet	0.40 ± 0.62	0.39 ± 0.68	0.945

Adapted from Tallman, et al. *Nutrients*, 2020 12(3), 797.

Values are mean ±SD; n=47 for hiSSB and 54 for the loSSB group. %TE food: the percentage total energy contribution from food.

Table 17: Patient Characteristics at Baseline According to Diet Cluster

	All (n = 100)	hiSSB (n = 47)	loSSB (n = 53)	*p* value between groups
Age, y	60 [53 - 68]	59 ± 12	60 ± 14	0.662
Males, n (%)	59 (59)	29 (29)	30 (30)	0.605
BMI, kg/m^2	27.4 [23.3 - 31.4]	29.7 ± 6.7	26.9 ± 6.0	**0.029**
Vintage (months)	45 [19 - 88]	62 ± 57	66 ± 68	0.770
Obese (BMI > 30), %	36 (36)	19 (19)	16 (16)	0.284
DM, n (%)	57 (57)	28 (28)	29 (29)	0.624
Tobacco Use, n (%)	29 (29)	14 (14)	15 (15)	0.870
[2]Kt/V	1.5 [1.4 - 1.6]	1.5 ± 0.2	1.6 ± 0.3	0.084
Antidepressant use, %	17 (17)	12 (12)	5 (5)	**0.032**
Renal vitamin* use, %	56 (56)	24 (24)	32 (32)	0.349
Serum Potassium (mEq/L)	4.6 [4.1 - 5.1]	4.7 ± 0.6	4.6 ± 0.6	0.632
Serum Phosphorus (mg/dL)	5.0 [4.3 - 5.8]	5.2 ± 1.5	5.0 ± 1.0	0.285
[3]Serum Albumin (g/dL)	3.8 [3.6 - 4.0]	3.8 ± 0.4	3.8 ± 0.3	0.948
[4]CRP (mg/L)	6.1 [3.1 - 8.4]	6.2 ± 4.8	6.0 ± 3.2	0.745
[4]IL-6 (pg/mL)	1.7 [0.01 - 5.3]	10.9 ± 36.7	13.2 ± 54.4	0.799
[5]IL-18 (pg/mL)	238 [172 - 320]	276 ± 146	259 ± 163	0.594
[4]MCP-1 (pg/mL)	113 [89 - 160]	155 ± 127	134 ± 97	0.373
Total Cholesterol (mg/dL)	148 [113 - 188]	147 ± 41	154 ± 47	0.471
Triglycerides (mg/dL)	81 [53 - 125]	106 ± 52	87 ± 51	0.069
LDL-C (mg/dL)	76 [46 - 104]	80 ± 34	80 ± 45	0.987
HDL-C (mg/dL)	47 [39 - 62]	46 ± 16	56 ± 21	**0.007**
Large HDL (mg/dL)	17.0 [11.0 – 31.8]	17.9 ± 12.7	27.2 ± 17.8	**0.003**
Intermediate HDL (mg/dL)	23.0 [18.3 – 26.0]	21.7 ± 5.4	23.8 ± 6.1	0.081
Small HDL (mg/dL)	6.0 [4.0 – 8.0]	6.7 ± 3.1	5.5 ± 3.4	0.076
[6]Large LDL(mg/dL)	20.5 [14.0 – 28.0]	20.4 ± 9.2	23.2 ± 10.1	0.154
[6] Intermediate LDL (mg/dL)	11.0 [7.0 – 16.0]	13.7 ± 7.8	11.8 ± 8.4	0.251
[6]Small LDL (mg/dL)	2.0 [0.0 – 5.3]	4.9 ± 6.1	3.1 ± 4.8	0.103
[6]Mean LDL Size (Å)	270.0 [266.0 – 273.0]	268.0 ± 4.6	270.3 ± 4.1	**0.009**
LDL Pattern A, n (%)	62 (61.4)	22 (21.8)	40 (39.6)	**0.050**
LDL Pattern B, n (%)	16 (15.8)	10 (9.9)	6 (5.9)	**0.050**

Adapted from Tallman, et al. *Nutrients*, 2020 12(3), 797.

Values are expressed as median [interquartile range (IQR)], means ± SDs, or percentages. Statistics: 2-sample *t* test, or Pearson chi-square test. BMI: Body Mass Index; DM, diabetes mellitus; Kt/V is a number used to quantify hemodialysis (K, dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea, approximately equal to patient's total body water); *Renal vitamins included Nephrocaps, Renal Caps, and Nephrovite brands; CRP: C-reactive protein; IL-6: Interleukin 6; IL-18: Interleukin 18; MCP-1: Monocyte Chemoattractant Protein-1; HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; Å: angstrom; [1]BP hiSSB (n=44), loSSB (n=43) [2]Kt/V hiSSB (n=43), loSSB (n=45); [3]Albumin hiSSB (n=46), loSSB (n=50); [4]CRP, [4]IL-6, [4]MCP-1 hiSSB (n=46), loSSB (n=52); [5]IL-18 hiSSB (n=46), loSSB (n=49); [6] large, [6] intermediate, and [6] small LDL, [6] mean LDL size and [6]LDL pattern hiSSB (n=46), loSSB (n=52).

Table 18: Mean Daily Nutrient Intake According to Diet Cluster

Nutrient	All (n = 100)	hiSSB (n = 47)	loSSB (n = 53)	*p* value between groups	Nutrient Recommendations
Energy, kcals	2027 ± 414	2123 ± 432	1941 ± 381	**0.029**	Per renal Rx
Protein, g	86 ± 26	83 ± 21	88 ± 29	0.311	Per renal Rx
% kcals from protein	17 ± 4	16 ± 4	18 ± 4	**0.008**	10-35*
Fat, g	90 ± 24	89 ± 25	91 ± 24	0.713	
% kcals from fat	40 ± 7	38 ± 6	42 ± 7	**0.001**	20-35*
CHO, g	218 ± 65	249 ± 68	191 ± 50	**< 0.001**	
% kcals from CHO	43 ± 8	47 ± 7	40 ± 7	**< 0.001**	45-65*
Fiber, g	12 ± 4	13.2 ± 3.9	11.8 ± 4.5	0.095	30*
Sugars, g	87 ± 45	115 ± 47	63 ± 23	**< 0.001**	< 50**
Phosphorus, mg	833 ± 303	797 ± 260	864 ± 335	0.263	Per renal Rx
Iron, g	11.5 ± 4.5	11.3 ± 4.1	11.6 ± 4.9	0.800	Per renal Rx
Magnesium, mg	149 ± 64	150 ± 65	147 ± 64	0.852	420*
Sodium, mg	2996 ± 961	3036 ± 1013	2960 ± 921	0.695	< 2300**
Potassium, mg	1500 ± 585	1487 ± 636	1512 ± 542	0.834	Per renal Rx
Zinc, mg	8.5 ± 4.1	7.4 ± 2.9	9.4 ± 4.8	**0.017**	11*
Vitamin C, mg	58 ± 46	69 ± 55	48 ± 33	**0.023**	90*
Vitamin E, mg	4.3 ± 3.1	4.4 ± 3.4	4.1 ± 2.9	0.628	15*
Chromium (µg)	4.4 ± 6.9	2.9 ± 4.5	5.7 ± 8.2	**0.031**	30*
Selenium (µg)	88.2 ± 37.8	79.6 ± 35.3	95.8 ± 38.7	**0.023**	55*
Folic acid, mg	225 ± 108	230 ± 112	221 ± 105	0.707	400*
Cholesterol, mg	412 ± 177	368 ± 153	452 ± 188	**0.016**	Per renal Rx or (< 200) [89]
My plate recommendations (%)					
Grain	76 ± 33	75 ± 37	77 ± 30	0.749	Based on age and gender [271]
Vegetable	33 ± 27	30 ± 25	35 ± 28	0.369	
Fruit	24 ± 33	32 ± 41	16 ± 21	**0.023**	
Dairy	13 ± 14	15 ± 14	12 ± 15	0.306	
Protein	148 ± 64	132 ± 59	162 ± 65	**0.019**	

Adapted from Tallman, et al. *Nutrients*, 2020 12(3), 797.

Values are means ± SDs, or percentages. Statistics: 2-sample *t* test, or Pearson chi-square test. *DRI, Dietary Reference Intakes for males ages 51-70 [154]; CHO, carbohydrate; Rx, prescription; **2015-2020 Dietary Guidelines for Americans recommends < 10 percent of calories per day from added sugars or 50 grams for a 2000 kcals [268].

Table 19: Comparison of KDQOL Score by Selected Variables

Variable	Symptoms	Effects	Burden	PCS	MCS
Diet Cluster					
hiSSB	73.8±13.1	74.1±17.7	48.8±26.7	33.5±11.1	46.1±12.7[a]
loSSB	79.2±10.7	81.1±15.6	64.8±29.0	36.5±11.0	53.0± 9.2[a]
Gender					
Male	77.4±11.6	78.2±16.8	56.3±28.6	35.4±11.7	50.7±12.5
Female	76.5±12.6	78.1±17.1	59.8±29.7	35.0±10.3	50.6±10.0
Tobacco use					
Yes	74.8±14.1	77.9±21.5	56.3±33.2	35.0±10.7	50.6±12.6
No	77.9±10.9	78.3±14.4	58.5±27.1	35.3±11.3	50.7±11.0
Antidepressant use					
Yes	66.1±17.6	66.3±24.9	42.5±29.1	28.0±9.2	43.6±10.9
No	78.2±10.7	79.6±15.3	59.6±28.6	36.1±11.0	51.5±11.3
Age [β(se)]	0.36(0.15)*	0.52(0.19)*	0.32(0.36)	0.03(0.13)	0.27(0.14)
Vintage [β(se)]	-0.03(0.03)	0.06(0.03)	0.13(0.06)*	-0.06(0.02)*	0.01(0.02)
BMI [β(se)]	-0.03(0.35)	-0.20(0.45)	0.56(0.80)	-0.35(0.28)	-0.46(0.30)

Adapted from Tallman, et al. *Nutrients*, 2020 12(3), 797.

[a] significant difference at 0.05. *significant association at 0.05. Values are mean ± SD. BMI: Body Mass Index.

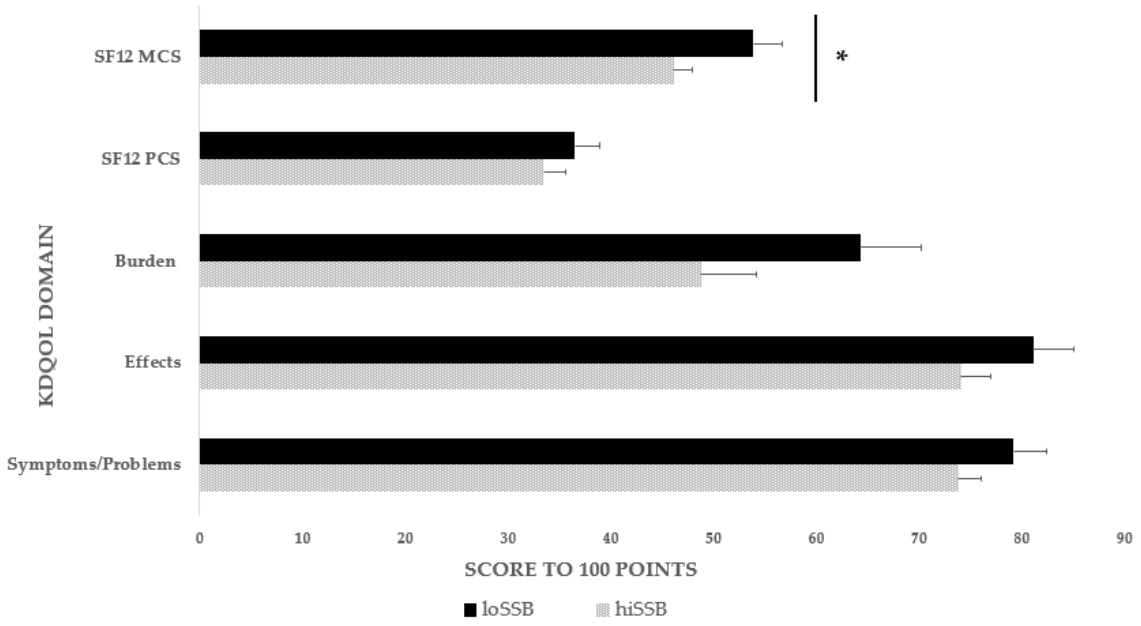


Figure 12: KDQOL Scores According to Diet Cluster

Adapted from Tallman, et al. *Nutrients*, 2020 12(3), 797.

SF 12 MCS: short form mental component summary; SF 12: short form physical component summary. Data is presented as means ± SEM. In comparison with patients consuming a loSSB pattern, those consuming a hiSSB pattern reported lower baseline KDQOL scores across all five domains and significantly lower baseline KDQOL scores for the S12 mental composite subscale. hiSSB, n=20; loSSB, n=28. Data were compared using a Mann-Whitney U test with a $*p < 0.05$ considered significant.

CHAPTER 5: RESULTS – SPECIFIC AIM THREE: TO ASSESS THE EFFECT OF NUTRITION AND HEALTH STATUS IN A COHORT OF AFRICAN AMERICAN MAINTENANCE HEMODIALYSIS PATIENTS ON MORTALITY

As of June 2020, data on mortality has been collected for two of the five clinics: Great Lakes Dialysis and DaVita Kresge, for a total of 80 patients. Table 20 shows the differences in mortality between deceased and survived participants. Subjects who consumed the hiSSB diet were 1.62 95% CI (0.830 – 3.155) times more likely to die than those consuming the loSSB diet (not significant). Deceased subjects had significantly lower HDL-C and intermediate HDL cholesterol. Causes of death included cardiac arrest or congestive heart failure (22), stroke (2), sepsis (2) and COVID-19 (3).

Table 20: Mortality Data

	Deceased (n = 25)	Survived (n= 54)	*p* value between groups
Age (years)	60 ±12	58 ±13	0.450
Vintage (mo)	52 ±44	61 ±57	0.427
BMI (kg/m^2)	28.8 ±6.4	28.5 ±6.8	0.813
Serum Potassium (mEq/L)	4.4 ±0.6	4.6 ±0.6	0.135
Serum Phosphorus (mg/dL)	5.1 ±1.3	5.1 ±1.1	0.958
Serum Albumin (g/dL)	3.7 ± 0.3	3.8 ±0.3	0.278
Serum Creatinine (mg/dL)	8.1 ±2.7	9.5 ±2.6	**0.049**
CRP (mg/L)	7.3 ±6.0	6.0 ±3.1	0.308
IL-6 (pg/mL)	4.0 ±5.7	20.1 ±63.2	0.075
IL-18 (pg/mL)	258 ±115	269 ±184	0.744
MCP-1 (pg/mL)	138 ±57	156 ±144	0.445
Total Cholesterol (mg/dL)	152 ± 47	152 ±45	0.976
Triglycerides (mg/dL)	107 ±63	91 ±45	0.242
LDL-C (mg/dL)	85 ±38	81 ±43	0.642
HDL-C (mg/dL)	45 ±13	53 ±19	**0.031**
Large HDL (mg/dL)	18.28 ±12.09	23.93 ±16.42	0.091
Intermediate HDL (mg/dL)	20.32 ±4.64	23.52 ±5.79	**0.011**
Small HDL (mg/dL)	6.32 ±3.11	5.98 ±3.48	0.666
Large LDL (mg/dL)	21.38 ±9.94	22.58 ±10.16	0.626
Intermediate LDL (mg/dL)	14.25 ±7.87	13.04 ±8.63	0.547
Small LDL (mg/dL)	4.88 ±5.93	4.00 ±5.61	0.545
Mean LDL Size (Å)	268 ±5.0	270 ±4.0	0.091
HiSSB, n (%)	15 (39)	26 (61)	0.150
LoSSB, n (%)	10 (24)	31 (76)	

Values are expressed as means ± SDs, or percentages. Statistics: 2-sample t test, or Pearson chi-square test.

CHAPTER 6: DISCUSSION

Characteristics of the Overall Study Population

The mean Kt/V for the entire cohort exceeded the minimum CMS quality standard of 1.2 [272]. Mean blood pressures reported for this cohort could not be compared to a standard as specific targets are not currently recommended per the 2006 KDOQI Clinical Practice Guidelines [273].

Mean serum ferritin for all patients was 757 ± 355 ng/mL; the 2001 KDOQI guidelines recommended keeping serum ferritin at < 800 ng/mL [274]; however, in 2006, the guidelines were updated to a target of < 500 ng/mL [275]. Analyses from the United States Dialysis Outcomes and Practice Patterns Study reported a mean serum ferritin increase from 601 ng/mL in 2009 to 887 ng/mL in 2012 across facilities operated by two large dialysis organizations in the U.S. [276]. Higher serum ferritin levels observed among HD patients in the U.S., including this cohort, are most likely resultant from the 2011 CMS bundled payment system, which included erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron [277].

In this cohort, the mean hemoglobin levels met the 2007 KDOQI target guidelines of 11.0 to 12.0 g/dL for HD patients receiving ESA therapy [275]. Mean serum potassium levels were found to be in an optimal range between 4.6 and 5.3 mEq/L [278]. Mean serum phosphorus was also within the normal recommended range of 3.5 and 5.5 mg/dL [146]. However, mean serum albumin was 3.8 ± 0.3 g/dL, which fell slightly below the KDOQI practice guideline recommendations of 4.0 g/dL [258].

Anthropometrics

In this study, female HD patients were found to have a significantly higher BMI than males; however, TSF and MAMC did not differ between genders, and serum creatinine levels were actually higher for males. Anthropometry is often used to assess nutritional status; however, it is

not always a good indicator of muscle mass for obese patients. Serum creatinine, which has been shown to correlate closely with muscle mass in dialysis patients, may be a superior measure [279]. Furthermore, a significant association was found between HGS and serum creatinine, suggesting that these two measures may reflect lean body mass better than MAMC for this group. Serum creatinine and HGS may be a more reliable measurement to detect changes in muscle mass for patients with BMI > 30 kg/m^2.

Only 5% of the patients in this cohort met three out of the four criteria for PEW. Given those patients too ill to enroll in PATCH would have met exclusion criteria, PEW prevalence may have been underestimated in this AA MHD population. However, 27% of males and 19% of females met the criteria for probable sarcopenia, which may be reflective of the advanced age of this group.

Dyslipidemia and Inflammation

In comparison to males, female patients presented with significantly higher TC, HDL-C, and large and intermediate HDL and large LDL subfractions. Given macronutrient distributions were similar between both genders, differences in lipoprotein compositions were not likely influenced from dietary composition. This finding of higher HDL-C among females is consistent with literature for both HD and non CKD AA populations [280, 281].

Higher TG/HDL-C levels are risk factors for CV disease in the general population [282], whereas higher levels of this ratio have been paradoxically associated with CV and overall survival in ESRD HD patients. This contradiction may be explained by (1) non-traditional risk factors, such as oxidative stress and inflammation, potentially transforming HDL from an anti-inflammatory to proinflammatory particle, or (2) reflect higher levels of TG as an indicator of better nutritional

status [283]. Patients in this PATCH subset with TG/HDL-C levels greater than 3.8 tended (non-significantly) towards lower levels of inflammatory markers.

Lipoprotein analyses revealed that both large and intermediate HDL subfractions were more prevalent in contrast to small HDL subfractions. A shift from smaller to larger HDL subpopulations has been previously reported in ESRD patients on HD [83, 284].

IL-18 activates PI3K/Akt and MEK/ERK1/2 signaling pathways, contributing to the production of the chemokine MCP-1, which recruits inflammatory cells such as macrophages to produce IL-6 as illustrated in Figure 11 [48]. IL-18 was found to be moderately positively correlated with downstream molecules MCP-1 and IL-6, but not with CRP. As an acute phase protein produced in the liver, CRP is secreted in response to IL-6 signaling, and to a lesser extent, IL-1β and other pro-inflammatory cytokines [285]. 28% of IL-6 levels were below the detection limit of the assay, therefore null findings for an association between IL-6 and CRP may be due to assay sensitivity.

In the general population, women, persons with DM, and AA have higher levels of CRP [286]. However, AA HD patients with higher levels of CRP have been found to have a paradoxical survival advantage when compared to whites, but this advantage may be related to inflammation stemming from causes other than CVD. Additionally, AA may be more resilient to the effects of inflammation, potentially due to better nutritional status [117]. Preliminary mortality data show that higher HDL-C and intermediate HDL subfractions, and serum creatinine (a surrogate for LBM) were associated with a mortality benefit.

Egg Consumption and Health Outcomes

Negative outcomes on serum lipids, phosphorus, or PTH were not apparent between those who reported consuming eggs and non-consumers. However, there are several limitations in

interpreting this finding. First, given the observational nature of the study, causality cannot be determined. Second, foods eaten with eggs, and not eggs per se, may be responsible for any association. Third, non-consecutive 24-hr recalls, and not a food frequency questionnaire, was used to collect data; therefore, actual egg consumption may not have been accurately captured. Associations or correlations with outcomes and individual nutrients or foods may be the result of confounding or lurking variables.

DII and Health Outcomes

DII showed a mean score of 3.1 ± 1.1 with a range of -0.54 to 5.83, indicating this sample of AA MHD patients consume a proinflammatory diet. As a reference, the DII has been reported as +4.0 for a fast food diet and -4.0 for the Mediterranean diet [200]. Similar to the findings in this analysis, Kizil, et al. reported a mean DII score of 1.76 ± 1.26 (min, -0.37; max, 4.90) in a cross sectional study of 105 Turkish HD patients [287]. Studies by different investigators have shown inconsistent findings on associations between DII and inflammatory markers. High DII scores have been positively associated with increased levels of high-sensitivity CRP (hs-CRP) in a cohort of 2567 postmenopausal women in the Women's Health Initiative Observational Study [288]. Kizil, et al. also found significant increasing trends across the tertiles of DII for CRP [287]. However, in a Belgian cross-sectional study of 2524 generally healthy subjects, no significant associations were observed between the DII and hs-CRP [289]. Since 2015, the DII has been used in over 200 studies and has formed the basis for 12 meta-analyses. The research team responsible for developing the DII recently made improvements to the DII construct by developing the E-DII to solve the counteracting effect of negative correlations between energy density and nutrient density.

Given patients showed a preference for energy-dense, nutrient-poor foods, and because energy is a component of the DII, these negative correlations were likely a complication in this

analysis [290]. Furthermore, the inflammatory contribution from the diet may be overshadowed by the production of inflammatory molecules in the uremic milieu.

Dietary Pattern Analysis

This study was not only the first published research to report on dietary patterns for HD patients in the U.S., but also the first to examine dietary patterns with QOL in HD patients.

We found that only 3% of the entire study population consumed the minimum four to five daily servings of fruits and vegetables recommended by the USDA for women and men aged 31-50 [268]. Likely attributed to the low consumption of micronutrient rich foods, dietary intakes for Mg, Zn, Cr, fiber, folic acid, and vitamins E and C fell below RDA guidelines for both groups.

Low intakes of micronutrients have similarly been found in other studies. In a cross sectional study of 163 MHD patients (25% AA), plasma carotenoid levels were found to be markedly reduced, a potential contributing factor to CVD risk [291]. In a dietary pattern analysis of JHS participants, those consuming fast food diets had significantly lower serum concentrations of the carotenoids lutein plus zeaxanthin and alpha tocopherol [292]. Although this latter study did not include CKD participants, it examined typical dietary patterns and potential nutrient shortfalls observed in an AA population.

The percentage of calories from carbohydrates fell below the AMDR range for the loSSB group and was at the lower end of the range for the hiSSB group. Refined carbohydrates exceeded DGA guideline upper limits for both groups, who also failed to meet the USDA recommendations for grains.

Micronutrient intakes for Se, Zn, and Cr were significantly lower in the hiSSB cluster. Lower QOL indicators have been associated with low intakes of Zn and Se. Due to lower physical ability and fatigue in non-CKD patients, low Zn status has been associated with impaired QOL

[293, 294]. Zn deficiency can contribute to disturbances in taste (dysgeusia) and smell, which may lead to poor nutritional intake [295-297]. Low intakes of micronutrients such as Zn and Se may have contributed to the lower QOL scores observed in the hiSSB group.

Inadequate micronutrient intake may have played a role in the atherogenic pattern B phenotype, lower total HDL cholesterol and large HDL subfractions and tendency towards higher levels of inflammation observed the hiSSB group. The lower levels of large HDL subfractions observed in the hiSSB group may reflect failure of maturation of HDL_2 from HDL_3, potentially due to oxidative modification of HDL or impaired LCAT activity.

Low Zn status has been associated with inflammation and lipid peroxidation [298]. Lower Cr levels have been associated with malnutrition in HD patients [299], and with inflammation, increased cardiovascular risk, and lower levels of HDL in non-CKD populations [300, 301]. Higher rates of hospitalization and death among HD patients have been associated with lower concentrations of Se [302].

Although the burden of following a restrictive diet has the potential to impair QOL [303], HD patients who control their diet experience enhanced general health and wellbeing and reduced symptom burden [304]. Following a healthy diet has also been associated with improved QOL in non-dialysis groups [305, 306]. Both lower mental and physical health scores were associated with increased risk of cardiovascular events among blacks with hypertensive CKD in the African American Study of Kidney Disease and Hypertension. The lower QOL scores may have resulted from several factors including poor self-care, resulting in poor dietary compliance [307, 308]. Each 10-unit drop in the mental health score has been associated with a 12% higher death risk among AA HD patients.

In order to reduce phosphorus and potassium intake, HD patients are often instructed to avoid dairy products, fruits, vegetables, and whole grains. At the same time, they are encouraged to consume protein rich foods, such as HBV proteins. Sugar sweetened juices, "clear" sugar sweetened carbonated beverages, and higher fat non-dairy products are often suggested to supply phosphorus and potassium free calories. Efforts to restrict potassium, sodium, and phosphorus, are perhaps also inadvertently encouraging the intake of sugar sweetened beverages, which can have negative consequences.

There are several limitations in this study. First, it is unclear whether dietary patterns may have influenced QOL or if self-perceived QOL affected dietary choices; therefore, causality cannot be determined. Second, diet data was not collected for dialysis days, and may not represent usual intake. Finally, micronutrient values may have been underestimated, since not all commercial products in ESHA Food Processor SQL software package have complete information.

Mortality

Similar profiles for HDL subfractions were observed for both deceased patients and those consuming a hiSSB diet pattern. Trends in the HDL subfractions for the deceased patients as compared to the survived patients may be reflective of failure for maturation of HDL_3 to HDL_2 for the deceased patients. Given the preliminary data, small sample size, and observational nature of this analysis, it is too early to draw conclusions.

CHAPTER 7: CONCLUSIONS AND RECOMMENDATIONS

The nutritional assessment data analyzed in this study consisted of objective data, such as clinical chemistry, anthropometric measurements, and measures of dialysis adequacy and subjective data, including diet recalls and QOL. Three different approaches to analyzing diet data to document the extent to which diet is associated with health outcomes in AA MHD patients were examined. Each approach provided valuable insight into nutrient shortfalls for AA patients receiving HD and may be used to guide nutritional interventions.

In the first approach, a focus on macro and micronutrient intakes revealed that patients in this cohort consume a macronutrient distribution range of 43/17/40 for carbohydrate/protein/fat. It was found that intakes for sodium, phosphorus, and potassium exceeded recommended guidelines by 76%, 22%, and 82%, respectively, and almost all patients fell below recommended intakes for several micronutrients, including vitamins C, E, K, zinc, and magnesium. It was also found that eggs, a food which is often limited due to phosphorus and cholesterol concerns, only accounted for approximately 2-3% of the total energy intake for this AA HD population. No differences were found for BMI, serum lipids, phosphorus, albumin, and PTH between those participants who reported any egg consumption against those who did not report egg consumption.

Using an *à priori* approach to calculate the Dietary Inflammatory Index showed that this group of patients consumed a proinflammatory diet, driven by low intakes of PUFA. After dichotomizing the DII, no associations were found between plasma inflammatory biomarkers and the higher DII group; however, with a homogenous population, the ability to robustly detect differences between groups may have been impacted.

The third approach used an *à posteriori* method to derive dietary patterns driven by the dietary data using a multivariate statistical technique. One important advantage of the *à posteriori* approach is that it takes into account all aspects of the diet rather than focusing on predefined food

groups or dietary indices, such as the DII. Two clusters were identified, revealing that lower KDQOL scores were associated with a dietary pattern characterized by high intakes of sugar sweetened beverages and reduced intakes of protein foods and vegetables. Those patients in the high sugar sweetened beverage cluster were found to have significantly lower intakes of several micronutrients, including Zn, Cr, and Se, which may have potentially contributed to the lower KDQOL scores as well as lower levels of HDL cholesterol and large HDL subfractions observed.

All dietary analyses demonstrated that the majority of patients consumed an energy dense diet, deficient in several micronutrients as most calories were derived from sugar sweetened beverages and processed foods. Dietary patterns high in sugar sweetened beverages were found to associate with negative health outcomes, including lower HDL-C, large HDL, mean LDL particle size, higher BMI, and lower QOL scores. On the other hand, eggs, which may be limited in renal diets due to phosphorus and cholesterol concerns, were not found to associate with negative health outcomes.

Preventing nutrient shortfalls while ensuring adequate calories and protein while avoiding excess intakes of phosphorus, potassium, and sodium remains a challenge. Providing nutritional supplements may help bridge the gap for some nutrients, although HD patients are typically prescribed renal specific vitamins, they provide only water-soluble B vitamins and vitamin C lost through dialysis. Only a few renal specific vitamins provide additional micronutrients such as Zn, Se, and vitamin E. Using a whole diet approach instead of focusing on individual nutrients may not only improve the QOL for many renal patients who find following a restrictive diet a burden, and thus abandons the diet altogether, but may also have a positive impact on other aspects of health, such as lipoprotein profile, muscle mass, and inflammation.

Further studies examining the impact of liberalizing the renal diet to include more whole foods and fewer processed foods on health outcomes in a controlled setting with close monitoring of nutrition and health indices are needed.

Additionally, the mortality benefit observed in the AA HD population is still unknown. Further studies examining longevity benefit related to muscle mass, fat mass, genetics, psychosocial status, inflammation, differences in mineral metabolism, vitamin D analogs dosage, lipoprotein profiles, dietary patterns, and CVD should be conducted.

Examination into obstacles encountered by AA HD patients in following renal diet restrictions, such as lack of access to healthy foods, reliance on ultra-processed foods, self-efficacy, and personal motivation may inform future interventions.

In light of advancements in HD procedures and new pharmacological interventions, the benefit of adhering to renal dietary restrictions versus risk of PEW, inadequate micronutrient consumption, lower QOL, and subsequent reliance on sugar sweetened and processed foods should be examined.

APPENDIX A: CASE REPORT FORM

Effects of Supplementing Palm Tocotrienols in Chronic Hemodialysis (PATCH)

IRB#123314MP4F
Screening and Baseline CRF Checklist

		Date Completed	Initials
☐	Personal Details & Medical History	_____	_____
☐	Medication Profile & Hemodialysis Regimen	_____	_____
☐	Anthropometry, Body Comp & Muscle Strength	_____	_____
☐	Biochemical Data	_____	_____
☐	24 Hour Recall	_____	_____
☐	Appetite and Diet Assessment Tool (ADAT)	_____	_____
☐	Restless Legs Syndrome Rating Scale	_____	_____
☐	KDQOL	_____	_____

Subject Number:

Center Information:

☐DaVita Kresge Dialysis
☐Great Lakes Dialysis, LLC
☐DaVita Highland Park Dialysis
☐Henry Ford Fairlane
☐DaVita Redford Dialysis
☐Henry Ford West Pavilion

INCLUSION CRITERIA

	Yes	No
1. Patient is willing and able to give informed consent for participation in the trial.	☐	☐
2. Male or Female, aged 18 years and above. Undergoing chronic hemodialysis treatment for more than 3 months (life expectancy > 1 year).	☐	☐
3. Able and willing to comply with all trial requirements.	☐	☐
4. Willing to allow his or her /Physician/Nephrologist/General Practitioner and consultant, if appropriate, to be notified of participation in the trial.	☐	☐

If the answer to any of the questions above is **no**, the participant is not eligible

EXCLUSION CRITERIA

	Yes	No
1. Participants who have participated in another research trial involving an investigational product in the past 12 weeks	☐	☐
2. History of functional kidney transplant 6 months before study entry; anticipated live donor kidney transplant over the study duration;	☐	☐
3. Participants who are taking vitamin E- containing supplements >60 IU/d during the past 30 days	☐	☐
4. History of poor adherence to hemodialysis or medical regimen	☐	☐
5. Participants who are currently on active treatment for cancer, excluding basal cell carcinoma of the skin	☐	☐
6. Participants who have been diagnosed as HIV/AIDS and/or on the anti-HIV therapy. (HIV seropositivity is not an exclusion criterion)	☐	☐
7. Patients taking anti-inflammatory medication, except aspirin<325 mg/d, over the past 30 days	☐	☐
8. Female participant who is pregnant, lactating or planning pregnancy during the course of the trial	☐	☐
9. Participants who are receiving nutritional support (i.e. enteral and intra-venous route)	☐	☐
10. Patients using a temporary catheter for dialysis access at baseline or patients receiving a graft/fistula within the 6-month study period	☐	☐
11. More than two hospitalizations within the last 90 days or one hospitalization within the 30 days preceding enrollment	☐	☐
12. Any other significant disease or disorder which, in the opinion of their nephrologist, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.	☐	☐

If the answer to any of the questions above is **yes**, the participant is not eligible

PERSONAL DETAILS

Dialysis Shift: ☐ Mon/Wed/Fri ☐Tues/Thurs/Sat

Time of Dialysis Shift: _____am/pm Duration: _____ hrs.

Gender: M/F Age:_____years old

Date of Birth (dd/mm/yy): _____

Ethnicity: ☐Caucasian ☐African American ☐Hispanic/Latino
☐Asian ☐Other: _____

MEDICAL HISTORY

What is the cause of kidney failure?

☐Unknown ☐Nephronophthisis
☐Diabetes Mellitus ☐APKD (Adult Polycystic Kidney Disease)
☐Hypertension ☐Gout Nephropathy
☐HIV-Nephropathy ☐Toxic Nephropathy
☐Kidney Stone ☐SLE (Systemic Lupus Erythematosus)
☐Glomerulonephritis ☐Others: _____

Start Date of HD: (mm/yy) _____/_____

Kidney Transplantation? ☐Yes ☐No
Parathyroid Gland Removed? ☐Yes ☐No

Current Diagnoses:
Diabetes? ☐Yes ☐No
Tobacco Use? ☐Yes ☐No
Secondary HPTH? ☐Yes ☐No
Hepatitis C ? ☐Yes ☐No

MEDICATION PROFILE

Prescribed Medications	Name	Dosage/Frequency
Renal vitamin/supplement		
Lactulose		
Calcium (carbonate/acetate)		
Sevelamer		
Lanthanum		
Other P binder		
Calcimimetic		
Iron		
Vitamin D		
ESA		
Insulin		
OHA		
Statin		
Ca channel blocker		
Alpha/beta blocker		
ACE inhibitor/ARB		
Others:		

HEMODIALYSIS PRESCRIPTION

Is the dialyzer reused? Yes, How often? _____Times ☐No

Type of dialyzer membrane: Polysulfone Cellulose triacetate Other: _____

Types of vascular graft being used: ☐Arterio venous fistula

☐Arteriovenous graft (AVG)

☐Venous Catheter

Type of dialysate buffer: ☐Acetate

☐Low calcium ☐Normal Calcium

☐High Calcium ☐Bicarbonate

ANTHROPOMETRIC DATA

Measurements	Date
Target Weight (kg)	
Height (cm)	
Post dialysis weight (dry weight)	
Body Mass index (kg/m^2)	
Average IDWG	
Average UFR	
Average BP	

MUSCLE STRENGTH

Hand Grip Dynamometer

Hand Grip Strength (kg)							
Left (L) or Right (R) hand	Dominant Hand	Avg	SD	CV	Test #1	Test #2	Test #3

BODY COMPOSITION -- MUSCLE MASS MEASUREMENTS

	1st measure	2nd measure	Mean
Mid-arm circumference (cm)			
Triceps skinfolds (mm)			

BIOCHEMICAL DATA

Renal Profile (Pre-Dialysis)	**Date**	**Test Result**	**Normal Range**
Pre BUN (mg/dL)			
Post BUN (mg/dL)			
Creatinine (mg/dL)			
Sodium (mEq/L)			
Potassium (mEq/L)			
Corrected Calcium (mg/dL)			
Phosphorus (mg/dL)			
Serum Albumin (g/dL)			
Total Cholesterol (mg/dL			
Triglycerides (mg/dL)			
HDL-C (mg/dL)			
LDL-C (mg/dL)			
Glucose (mg/dL)			
HgbA1C (g/dL)			
Hemoglobin (g/dL)			
Hematocrit (%)			
Serum Fe (µg/dL)			
Serum TIBC (µg/dL)			
TSAT (%)			
Ferritin (ng/mL)			
Kt/V			
URR			
nPCR (g/kg/day)			
hsCRP (mg/L)			
PTH			
WBC			
Vit D			

24-hour dietary recall				Dialysis Day or Non-Dialysis day	
Meal	**Home (H)/Outside of Home (O)**	**Food Eaten**	**Quantity (c, tsp. oz., g)**	**Preparation Method (fried, grilled, roasted, stewed)**	**Source of food (fresh, frozen, canned, etc.)**

APPETITE AND DIET ASSESSMENT TOOL (ADAT)

During the past week (7 days), how would you rate your appetite?

1 = Very Good
2 = Good
3 = Fair
4 = Poor
5 = Very Poor

2. Have you had a change of appetite in the past week (7 days?)

0 = no
1 = Yes

3. If you answered “yes” to #2, how has your appetite changed?

1 = Increased
2 = Remained the same
3 = Decrease

APPENDIX B: DIETARY ANALYSIS OUTPUT EXAMPLE

Spreadsheet

Item Name	Quantity	Measure	Cals (kcal)	Prot (g)	Carb (g)	TotFib (g)	Sugar (g)	SugAdd (g)	Fat (g)	SatFat (g)	MonoFat (g)
Day 2 (1/11/2018)			1978.04	102.99	226.93	9.83	48.67	0	72.37	24.62	22.79
Breakfast			538.50	18.63	68.15	2.57	21.60	0	21.74	10.28	6.95
cereal, corn flakes	1	Cup	99.96	2.10	23.55	0.92	2.66	--	0.11	0.03	0.02
bacon, pan fried, cured	2	Slice	107.64	7.80	0.39	0	0	0	8.07	2.75	3.57
bread, soft white, toasted	2	Slice	127.60	3.96	23.98	1.28	2.73	--	1.76	0.34	0.35
juice, orange, chilled	4	Fluid ounce	61.01	0.85	14.37	0.37	10.35	--	0.15	0.02	0.03
butter, salted	2	Teaspoon	67.88	0.08	0.01	0	0.01	0	7.68	4.86	1.99
milk, whole, 3.25%, with vitamin D	0.5	Cup	74.42	3.84	5.86	0	5.86	0	3.97	2.28	0.99
Lunch			716.40	27.16	98.19	5.41	18.34	0	24.31	6.13	7.14
bread, soft white	2	Slice	154.28	5.13	28.66	1.57	3.29	--	1.93	0.40	0.35
hamburger, regular patty	4	Ounce-w...	298.24	15.08	33.53	2.04	6.75	--	11.54	4.04	4.38
salad mix, classic iceberg	1	Cup	10.00	0.67	2.67	0.67	1.33	0	0	0	0
salad dressing, french	1	Tablespoon	73.12	0.12	2.49	0	2.49	--	7.17	0.90	1.35
ketchup	1	Teaspoon	5.00	0	1.33	0	1.33	--	0	0	0
roll, dinner, large	2	Ounce-w...	175.77	6.16	29.51	1.13	3.15	--	3.67	0.78	1.07
soda, diet, Vernors	6	Fluid ounce	0	0	0	0	0	0	0	0	0
Dinner			653.14	56.69	50.09	1.84	3.24	0	23.32	7.46	8.19
chicken leg, roasted, skinless	1	Each	346.26	48.20	0	0	0	0	15.52	4.19	6.07
rice, white, cooked, parboiled, long grain, enriched	0.5	Cup	97.17	2.30	20.58	0.71	0.09	0	0.29	0.06	0.06
roll, dinner, large	2	Ounce-w...	175.77	6.16	29.51	1.13	3.15	--	3.67	0.78	1.07
soda, diet, Vernors	6	Fluid ounce	0	0	0	0	0	0	0	0	0
butter, salted	1	Teaspoon	33.94	0.04	0.00	0	0.00	0	3.84	2.43	0.99
Evening Snack			70.00	0.50	10.50	0	5.50	--	3.00	0.75	0.50
cookie, wafer, vanilla, Nilla	4	Each	70.00	0.50	10.50	0	5.50	--	3.00	0.75	0.50

Note: Partial screenshot of ESHA Food Processor SQL software's dietary analysis spreadsheet report from one subject/one day's meal entry

APPENDIX C: KIDNEY DISEASE QUALITY OF LIFE (KDQOL) SURVEY

Your Health

– and –

Well-Being

Kidney Disease and Quality of Life (KDQOL™-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Thank you for completing these questions!

Study of Quality of Life For Patients on Dialysis

What is the purpose of the study?

This study is being carried out in cooperation with physicians and their patients. The purpose is to assess the quality of life of patients with kidney disease.

What will I be asked to do?

For this study, we want you to complete a survey today about your health, how you feel and your background.

Confidentiality of information?

We do not ask for your name. Your answers will be combined with those of other participants in reporting the findings of the study. Any information that would permit identification of you will be regarded as strictly confidential. In addition, all information collected will be used only for purposes of the study, and will not be disclosed or released for any other purpose without your prior consent.

How will participation benefit me?

The information you provide will tell us how you feel about your care and further understanding about the effects of medical care on the health of patients. This information will help to evaluate the care delivered.

Do I have to take part?

You do not have to fill out the survey and you can refuse to answer any question. Your decision to participate will not affect your opportunity to receive care.

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. **In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

	Yes, limited a lot	Yes, limited a little	No, not limited at all
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
3. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
4. Accomplished less than you would like	☐ 1	☐ 2
5. Were limited in the kind of work or other activities	☐ 1	☐ 2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
6. Accomplished less than you would like	☐ 1	☐ 2
7. Didn't do work or other activities as carefully as usual	☐ 1	☐ 2

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Your Kidney Disease

How true or false is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
13. My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the past 4 weeks, to what extent were you bothered by each of the following?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
17. Soreness in your muscles?	☐	☐	☐	☐	☐
18. Chest pain?	☐	☐	☐	☐	☐
19. Cramps?	☐	☐	☐	☐	☐
20. Itchy skin?	☐	☐	☐	☐	☐
21. Dry skin?	☐	☐	☐	☐	☐
22. Shortness of breath?	☐	☐	☐	☐	☐
23. Faintness or dizziness?	☐	☐	☐	☐	☐
24. Lack of appetite?	☐	☐	☐	☐	☐
25. Washed out or drained?	☐	☐	☐	☐	☐
26. Numbness in hands or feet?	☐	☐	☐	☐	☐
27. Nausea or upset stomach?	☐	☐	☐	☐	☐
28[a]. (Hemodialysis patient only) Problems with your access site?	☐	☐	☐	☐	☐
28[b]. (Peritoneal dialysis patient only) Problems with your catheter site?	☐	☐	☐	☐	☐

Effects of Kidney Disease on Your Daily Life

Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease <u>bother</u> you in each of the following areas?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
29. Fluid restriction?	☐	☐	☐	☐	☐
30. Dietary restriction?	☐	☐	☐	☐	☐
31. Your ability to work around the house?	☐	☐	☐	☐	☐
32. Your ability to travel?	☐	☐	☐	☐	☐
33. Being dependent on doctors and other medical staff?	☐	☐	☐	☐	☐
34. Stress or worries caused by kidney disease?	☐	☐	☐	☐	☐
35. Your sex life?	☐	☐	☐	☐	☐
36. Your personal appearance?	☐	☐	☐	☐	☐

Thank you for completing these questions!

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ABSTRACT

ASSESSMENT OF *À PRIORI* AND *À POSTERIORI* DERIVED DIETARY PATTERNS ON HEALTH OUTCOMES IN AFRICAN AMERICAN MAINTENANCE HEMODIALYSIS PATIENTS

by

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August 2020

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In the United States, African Americans (AA) suffer a disproportionate burden of ESRD, accounting for 35% of all dialysis patients, and are 3.7 times more likely to progress to ESRD than whites. This increase in CKD risk is partially attributed to higher rates of hypertension, diabetes mellitus, and cardiovascular disease. Paradoxically, once on hemodialysis, AA have a survival advantage over whites, likely due to multiple factors including nutritional status, inflammation, psychosocial status, and genetic variation.

Although both the dialysis procedure and pharmacological treatments are effective at reducing the uremic toxin load, HD patients are still encouraged to adhere to strict dietary guidelines. In an effort to avoid foods high in phosphorus and potassium, patients requiring HD have limited intakes of fruits, vegetables, nuts, legumes, dairy, and whole grains. Associated with reduced consumption of foods naturally rich in phytochemicals, such as carotenoids and polyphenols, is a potential for the loss of benefit from the antioxidant and anti-inflammatory activities associated with their intake.

ESRD patients on HD suffer from excessive oxidative stress, which has been associated with an increased risk for cardiovascular disease. Mortality due to CVD is 20 times higher than in

the general population due to both traditional and nontraditional risk factors such as protein energy wasting, insulin resistance, anemia, oxidative stress, and inflammation. The HD procedure itself results in a significant loss of antioxidants, while the bioincompatibility of dialyzers and dialysate trigger the production of free radicals.

Nutritional approaches to improve outcomes for ESRD patients on HD have evolved over time and reflect technological advances in renal replacement therapy. Focus in research has shifted from restriction of individual nutrients and foods to examining diet patterns associated with improved outcomes and mortality.

Two main analytical approaches used to identify dietary patterns in nutritional epidemiology are *à priori* (hypothesis-driven) and *à posteriori* (data-driven) methods. *À priori* methods are based on indices of diet quality or nutritional health defined scores and assess the extent to which a subject complies with the predefined dietary pattern, whereas *à posteriori* methods use multivariate statistical techniques to derive dietary patterns empirically based on the actual diet in a specific population.

Health outcomes in AA maintenance hemodialysis patients and derived dietary patterns using both an *à posteriori* and an *à priori* method were examined.

The Dietary Inflammatory Index (DII), *à priori* method, failed to show any correlation with inflammatory or anthropometric indices. DII showed a mean score of 3.1 ± 1.1 with a range of -0.54 to 5.83, indicating patients consumed a proinflammatory diet. The null association between diet and inflammatory markers (CRP, MCP-1, IL-6 and IL-18) may reflect that the inflammatory contribution from the diet is overshadowed by the production of inflammatory molecules in the uremic milieu.

A cluster analysis, an *à posteriori* method, was performed using the *k*-means algorithm, a nonhierarchical clustering method which classifies participants into non-overlapping groups based on Euclidean distance, to obtain dietary patterns. Two major dietary patterns were identified: (Cluster 1) a high "sugar sweetened beverage" pattern (hiSSB) and (Cluster 2) a low "sugar sweetened beverage" pattern (loSSB). The hiSSB dietary pattern was characterized by higher energy contributions from calorically sweetened soft and juice drinks ($p < 0.001$) and poultry ($p < 0.05$), whereas the greatest energy contributors to the loSSB group was unprocessed red meat ($p < 0.05$), fish and shellfish, ($p < 0.05$), and custard style desserts such as puddings, ice cream, and cheesecake ($p < 0.05$). Compared to those in the loSSB dietary pattern cluster, patients in the hiSSB cluster scored lower baseline values on all five KDQOL domains and significantly lower on the S12 mental composite domain ($p < 0.026$).

All dietary analyses demonstrated that the majority of patients consumed an energy dense diet, deficient in several micronutrients as most calories were derived from sugar sweetened beverages and processed foods. Future studies aimed at interventions to examine the effects of liberalizing the standard renal diet to deemphasize phosphorus and potassium rich foods and allow whole and minimally processed foods are needed.

AUTOBIOGRAPHICAL STATEMENT

Education

- B.S. in Dietetics, Michigan State University, East Lansing, MI (1994)
- A.A.S. in Culinary Arts, Schoolcraft College, Livonia, MI (2010)
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Professional Appointments

- LTC Dietitian, Oakland County Medical Care Facility, Pontiac, MI, (1996-2001)
- Clinical Dietitian, St. Marcy Mercy Hospital, Livonia, MI, (2001-2003)
- Consultant Dietitian, Chartwells Corporation, Rye Brook, NY, (2012-2013)
- Unidine Corporation, Boston, MA, (2014-2016)
- Graduate Teaching Assistant, Wayne State University, Detroit, MI (2016-2020)

Certification

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Publications

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