The impact of food processing and diet quality on nutrition management for adults living with kidney disease

by

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Abstract

Background: Food processing changes the health value and nutrient content of foods. In the general population, consumption of minimally processed foods is encouraged to reduce the intake of free sugar, fat and sodium and increase fibre, protein and potassium intake. Many nutritious foods are high in potassium and phosphorus. For adults living with chronic kidney disease (CKD) low potassium and phosphorus diets are recommended to prevent hyperkalemia and hyperphosphatemia, respectively. There is inherent friction between healthy diets and diets for CKD, though how food processing may either contribute to or alleviate this friction has not been well elucidated. The overarching objective of this research was to explore the impact of food processing on medical nutrition therapy and health outcomes for adults living with CKD.

Methods and Results: In **Study 1,** The United States Department of Agriculture's Branded Foods Product Database (USDA-BFPD) (n=239,089) was used to explore potassium and phosphate additive use in processed foods. Ingredient lists were searched for potassium and phosphorus additives. For products with potassium or phosphorus content available the relationship between additive use and mineral content was explored. In the USDA-BFPD potassium and phosphorus additives were found in 14.7% and 31.2% of foods, respectively. Potassium and phosphorus content were available for 5.5% and 1.5% of food items, respectively. Subset analysis showed that a greater proportion of foods with potassium additives were considered high or very high in potassium than in foods without potassium additives. Surprisingly, median phosphorus content was lowest in products with only added lecithin than in products without any phosphorus additives (86 (54-200) vs 145 (77-351) mg per 100g, $p<0.01$), which was not different from products with phosphate salts (176 (101-276) mg per 100g, $p=0.22$) or products with both phosphate salts and lecithin (161 (99-285) mg per 100g, $p=1.00$).

For all products, phosphorus and potassium content were correlated, but the relationship was stronger for products which contained potassium phosphate additive when compared to products without potassium phosphates (rho = 0.81 vs 0.53, $p < 0.05$). **Study 2** was a longitudinal study of adults living with diabetes and CKD (n=50). Six years of diet records were reviewed. Diet quality scores were calculated and processed food intake was quantified to investigate the relationship between diet quality and processed food intake with cardiovascular health, health related quality of life and nutritional adequacy. Over 61% of energy intake came from processed foods. Diet quality was not associated with blood lipids or glycemic control. High vs low diet quality was associated with improvements in mental and general health quality of life scores (84.4 ± 14.3 vs 80.3 ± 17.1, $p < 0.05$ and 62.6 ± 21.0 vs 56.3 ± 19.8, $p < 0.01$, respectively) and nutritional adequacy. **Study 3** was a cross-sectional study of adults living with advanced CKD (n=216). Diet histories were used to investigate the relationship between protein sources (plant/animal) and electrolyte disturbances, nutrition and health status. Data did not demonstrate a correlation between plant protein intake and hyperkalemia or hyperphosphatemia events. Those who consumed more plant proteins had higher diet quality and consumed more fibre.

Conclusions: The mineral content of processed foods is not well documented. However, when potassium and phosphorus additives are used these foods may be higher in potassium and/or phosphorus, respectively. Adults living with CKD consume significant amounts of processed foods. This consumption pattern was associated with a reduced nutrient adequacy and lower health related quality of life but not cardio-metabolic risk factors. There was not a relationship between increased plant protein intake and higher rates of hyperkalemia or hyperphosphatemia. Taken together, this suggests that restriction of minimally processed foods would benefit from

re-evaluation, though ultimately a safety study is needed to understand more about the impact of healthy foods on serum potassium and phosphorus levels.

Preface

This thesis is an original work by Kelly Picard. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board:

1) Vitamin D Supplementation and Bone Health in Adults with Diabetic Nephropathy, Pro00022639, 2011-2012.

2) Vitamin D Supplementation and Bone Health in Adults with Diabetic Nephropathy: A follow up study, Pro00049292, 2014-present.

2) Plant-based foods and serum phosphorus levels, Pro00084546, August 26, 2019-July 30, 2020

3) Plant-based diets and serum phosphorous levels, Pro00077347, January 2, 2018-April 25, 2018

Chapter 1 of this thesis includes excerpts from a manuscript published as "Picard K, Barreto Silva MI, Mager DR, & Richard C (2020). Dietary Potassium Intake and Risk of Chronic Kidney Disease Progression in Predialysis Patients with Chronic Kidney Disease: A Systematic Review. Advances in Nutrition, Volume 11, Issue 4, July 2020, Pages 1002–1015, DOI: https://doi.org/10.1093/advances/nmaa027". Kelly Picard and Caroline Richard conceptualized the article. Diana R Mager provided clinical and scientific expertise on CKD. Kelly Picard and Maria Ines Barreto Silva completed data extraction. Kelly Picard and Maria Ines Barreto Silva wrote the manuscript with the assistance of Caroline Richard and Diana Mager. All authors read and approved the final manuscript.

Chapter 1 of this includes excerpts from a manuscript published as "Picard K, Mager DR, Richard C (2021) The impact of protein type on phosphorus and nutrition status in patients with chronic kidney disease: a critical review. Advances in Nutrition. DOI: http://doi.org.10.1093/advances/nmab062." Kelly Picard, Caroline Richard and Diana R Mager conceptualized the article. Caroline Richard and Diana R Mager provided clinical and scientific expertise on CKD. Kelly Picard completed the search and data extraction. Kelly Picard wrote the manuscript with the assistance of Caroline Richard and Diana R Mager. All authors critically reviewed the manuscript and read and approved the final manuscript.

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data extraction. Kelly Picard and Melanie Griffiths wrote the manuscript with the assistance of Caroline Richard and Diana R Mager. All authors read and approved the final manuscript.

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Chapter 3 of this thesis includes excerpts from a manuscript published as "Picard K, Picard C, Mager DR, Richard C (2021). Potassium content of the American Food Supply and implications for the management of hyperkalemia in CKD: An analysis of the Branded Product Database. Seminars in Dialysis. DOI: https://doi.org/10.1111/sdi.13007". Kelly Picard and Caroline Richard conceptualized the article. Diana R Mager provided clinical and scientific expertise on CKD. Kelly Picard and Christopher Picard completed data extraction and analysis. Kelly Picard wrote the manuscript with the assistance of Christopher Picard, Caroline Richard and Diana R Mager. All authors read and approved the final manuscript.

Chapter 3 of this thesis includes excerpts from a manuscript with revisions submitted as “Picard K, Mager DR, Senior PA, Richard C. Potassium-based sodium substitutes and implications for those requiring concurrent sodium and potassium restricted diets. Journal of the Academy of Nutrition and Dietetics.” Kelly Picard and Caroline Richard conceptualized the article. Peter A Senior, Caroline Richard and Diana R Mager provided clinical and scientific expertise on CKD. Kelly Picard completed data analysis. All authors critically reviewed the manuscript and approved the final version of the manuscript to be submitted.

Chapter 3 of this thesis includes excerpts from a manuscript submitted as “Picard K, Griffiths M, Senior PA, Mager DR, Richard C. Phosphorus additives and their impact on phosphorus content in foods – an analysis of the USDAs Branded Foods Product Database. Journal of Renal Nutrition.” Kelly Picard and Melanie Griffiths conceptualized the article. Peter A Senior, Caroline Richard and Diana R Mager provided clinical and scientific expertise on CKD. Kelly Picard completed data analysis. All authors critically reviewed the manuscript and approved the final version of the manuscript to be submitted.

Chapter 4 of this thesis contains excerpts of a manuscript which has been published as “Picard K, Senior PA, Adame Perez S, Jindal K, Richard C, Mager DR. (2021). Low Mediterranean Diet scores are associated with reduced kidney function and health related quality of life but not other markers of cardiovascular risk in adults with diabetes and chronic kidney disease. Nutrition, Metabolism and Cardiovascular Disease 31(5), 1445-1453.” Diana R Mager, Caroline Richard and Kelly Picard conceptualized the article. Peter A Senior, Caroline Richard and Kailash Jindal provided clinical and scientific expertise on Diabetes, CKD and Mediterranean meal patterning.

Diana R Mager and Kelly Picard completed data analysis and co-wrote the manuscript. Stephanie Adame Perez participated in data collection, data analysis and critical review. All authors read and approved the final manuscript.

Chapter 4 of this thesis contains excerpts of a manuscript which has been published as "Picard K, Senior PA, Wilmott A, Jindal K, Richard C, Mager DR (2022). Comparison of diet quality tools to assess nutritional adequacy for adults living with kidney disease. Canadian Journal of Dietetics Practice and Research. DOI: https://doi.org/10.3148/cjdpr-2022-009". Diana R Mager, Caroline Richard and Kelly Picard conceptualized the article. Peter A Senior, Caroline Richard and Kailash Jindal provided clinical and scientific expertise on Diabetes, CKD and Mediterranean meal patterning. Diana R Mager and Kelly Picard completed data analysis and co-wrote the manuscript. Ashley Wilmott participated in data collection, data analysis and critical review. All authors read and approved the final manuscript.

Chapter 5 of this thesis has been submitted as "Picard K, Griffiths M, Dusterhoft J, Colebrook-Fonseca S, Senior PA, Mager DR, Richard C. The impact of protein source on serum potassium and phosphorus levels in adults living with advanced kidney disease. Nutrition, Metabolism and Cardiovascular Disease." Kelly Picard, Melanie Griffiths, Janelle Dusterhoft and Caroline Richard conceptualized and designed the study. Kelly Picard, Melanie Griffiths, Janelle Dusterhoft, Shonagh Colebrook-Fonseca and Caroline Richard were involved in recruitment, data collection and student supervision. Peter Senior and Diana Mager provided clinical and scientific expertise on CKD. Kelly Picard completed analysis with the assistance of Diana Mager and Caroline Ricard. Kelly Picard and Melanie Griffiths wrote the manuscript with the assistance

of Janelle Dusterhoft, Shonagh Colebrook-Fonseca, Peter Senior, Caroline Richard and Diana Mager. All authors read and approved the final manuscript.

Dedication

I would like to dedicate this work to adults living with kidney disease who I have worked with as a dietitian and as a student. To work with this population is truly a gift. Each day, I am amazed by the resilience of these individuals; to see how they find the bright side, no matter how daunting the road ahead lies, inspires me to attempt to find the same grace in my own daily life. Thank you to everyone who has shared their time, story and a piece of your life with me. I truly hope this work can make a difference in the lives of those living with kidney disease.

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I would like to acknowledge the support of my husband throughout this process, balancing work, kids and academic life wouldn't have been possible without Chris. I am thankful every day for the chance encounter that led our paths to cross. Life has been an adventure worth living with you. And finally, to Walter and Oscar, the two best boys in the world who bring my life meaning, depth and joy. Being your mom has been one of the most challenging and rewarding endeavors of my life and I can't wait to see your lives unfold.

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List of Abbreviations

ASA24 – Automated self-assessment 24

BMI – Body mass index

BFPD – Branded foods product database

CARI – Caring for Australians with Renal Impairment

CKD – chronic kidney disease

DASH – Dietary approaches to stop hypertension

DHQ3 – diet history questionnaire 3

FDA – Food and Drug Administration (United States Department of)

HEI – Healthy Eating Index

HFD – Healthy Food Diversity

g - gram

KDIGO – Kidney Disease Improving Global Outcomes

KDOQI – Kidney Disease Outcome Quality Initiative (National Kidney Foundation of America)

kg - kilogram

K - potassium

MDI – major depressive index

MDS – Mediterranean diet score

nPCR – normalized protein catabolic ratio

PBSS – Potassium based sodium substitute

PEN – Practice Based Evidence in Nutrition by Dietitians of Canada

PO4 – phosphorus

RAAS – renin angiotensin aldosterone system

RAASi – renin angiotensin aldosterone system inhibitor

SF-36 – short form 36 assessment of health-related quality of life

USDA – United States Department of Agriculture

List of Appendices

Chapter 1: Background

1.1 Introduction

In Canada consumption of processed foods is increasing while consumption of minimally processed foods is decreasing.[1] Higher intakes of processed foods is associated with higher intakes of sodium, refined sugars and saturated fats, which may be associated with chronic disease risk in the general population.[2,3] While it may be assumed that those with chronic diseases, such as kidney disease, will be at the same risk with this type of dietary pattern, this has yet to be established. This is because nutrition recommendations for kidney disease have traditionally deviated from nutrition recommendations for the general population to prevent hyperkalemia and hyperphosphatemia.

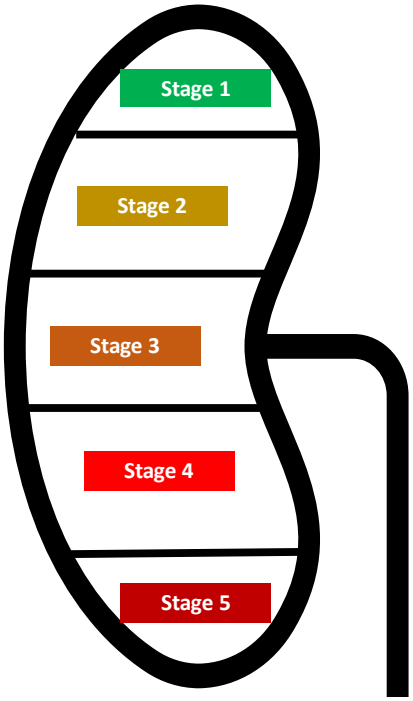
1.2 Chronic Kidney Disease (CKD)

1.2.1 Pathophysiology of CKD

Kidney disease impacts one in ten Canadians, and is considered the 12th leading cause of death globally.[4] CKD is a progressive disease comprised of 5 stages, with stage 1 being the earliest form of the disease and stage 5 the most advanced (**Figure 1.1**).[5] The kidney's primary function is maintenance of fluid and electrolyte balance and removal of waste products through urine formation. The main functional unit of the kidney is the nephron while the main vascular component is the glomerulus. Adequate blood supply is essential to kidney function, with approximately 22% of cardiac output destinated for the kidneys.[6] Given the complex nature of the kidneys, there are number of pathological milieu that can result in kidney damage. The four broad categories describing kidney disease etiology include glomerular diseases (such as

diabetes), tubulointerstitial diseases (such as obstructions), vascular diseases (such as hypertension) and cystic or congenital diseases (such as polycystic kidney disease).

Figure 1.1: The stages of kidney disease.[5] eGFR – estimated glomerular filtration rate (mL/min/1.73m^2)



Stage	eGFR	Description	Diet therapy
1	>90	Normal kidney function	General healthy diet
2	60-89	Mild function loss	Low sodium and protein
3	30-59	Moderate function loss	Low sodium, protein +/- low potassium, phosphorus
4	15-29	Severe function loss	Low sodium, protein, potassium, phosphorus
5	<15	Renal failure	High protein, low sodium, potassium, phosphorus

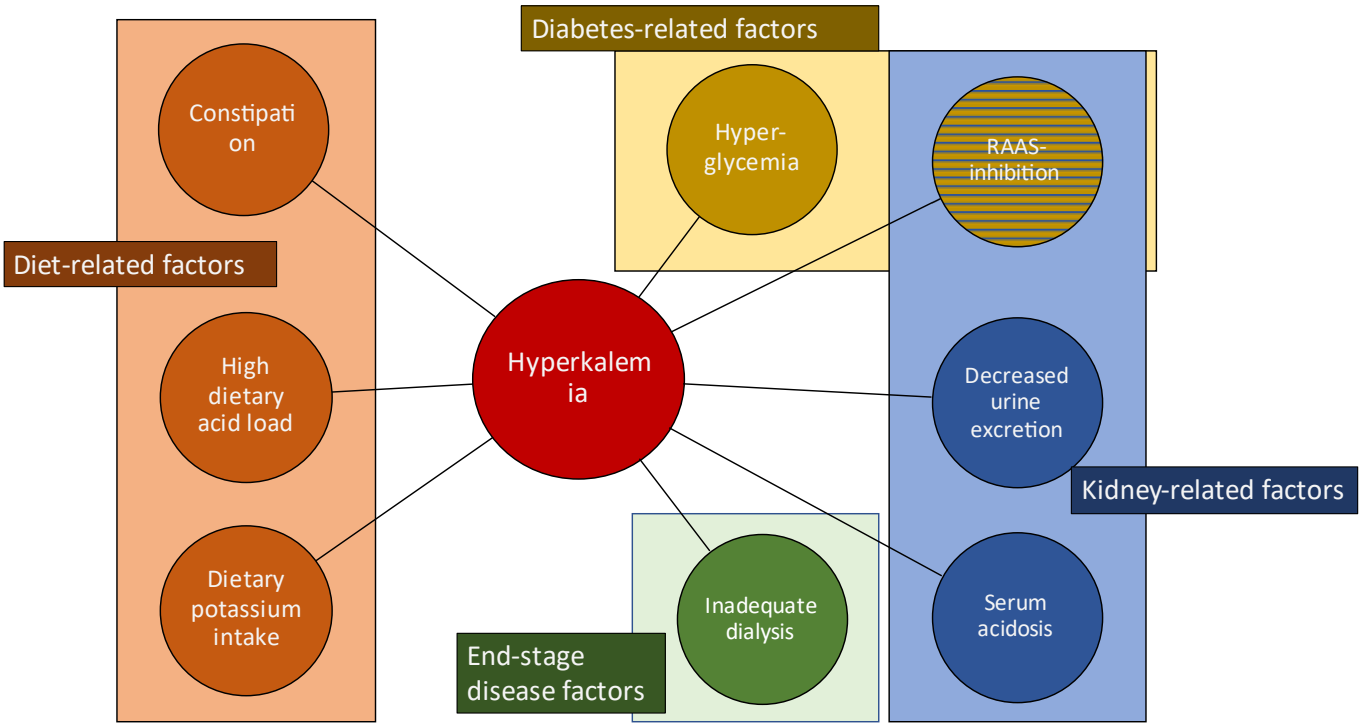
Diabetes is the leading cause of kidney disease. Hyperglycemia impacts kidney function through mechanical and metabolic pathways.[7] In the initial stages of diabetic kidney disease, mechanical changes are observed in the glomerular capillaries leading to hyperfiltration and microalbuminuria.[7] As the disease progresses thickening of several renal tissues, including in the glomerulus, tubules and arterioles occurs.[7] Metabolic impacts involve the inappropriate activation of the renin-angiotensin aldosterone system (RAAS) leading to increased glomerular capillary pressure.[8] RAAS regulates the amount of sodium in the body by secreting renin in response to a fall in the amount of sodium in the extracellular fluid or a reduction in blood pressure.[6] Activation of the RAAS system results in increased sodium reabsorption in the renal

tubules, in part facilitated by the sodium-potassium adenosine-triphosphatase carriers. As sodium is exchanged for potassium, there is an increased amount of potassium excreted in the urine.[9] As such, in addition to optimizing glycemic control, a group of medications known RAAS-inhibitors are recommended as first line of therapy for the prevention and management of diabetic nephropathy.[10]

1.2.2 Pathophysiology of hyperkalemia in kidney disease (including dialysis)

Decreased kidney function increases the risk of hyperkalemia through decreased urine potassium excretion[11] and changes in the RAAS.[8] However, potassium homeostasis is influenced by several factors.[11] Potassium is primarily an intra-cellular cation, that can be shifted into the extra-cellular space by several mechanisms.[11] For example, hyperglycemia or inadequate insulin can cause a shift of potassium out of the intra-cellular space and lead to hyperkalemia.[11] Extracellular acidosis, either related to decreased acid secretion in the urine, decreased bicarbonate absorption, decrease ammoniagenesis or respiratory acidosis will also shift potassium extra-cellularly. Additionally, high acid diets impact the amount of potassium in the intracellular and extracellular space. For those receiving dialysis therapy, inadequate dialysis related to missed or shortened treatments or poorly functioning dialysis access can also lead to hyperkalemia. Other diet factors, may include excess potassium intake or reduced fecal losses due to constipation from low fiber diets or fluid restrictions. Any of these factors can contribute to excess potassium in the blood and result in hyperkalemia (**Figure 1.2**). Hyperkalemia is a potentially fatal complication of kidney disease, associated with an increased risk of cardiac arrythmias.[12]

Figure 1.2: Factors contributing to hyperkalemia.

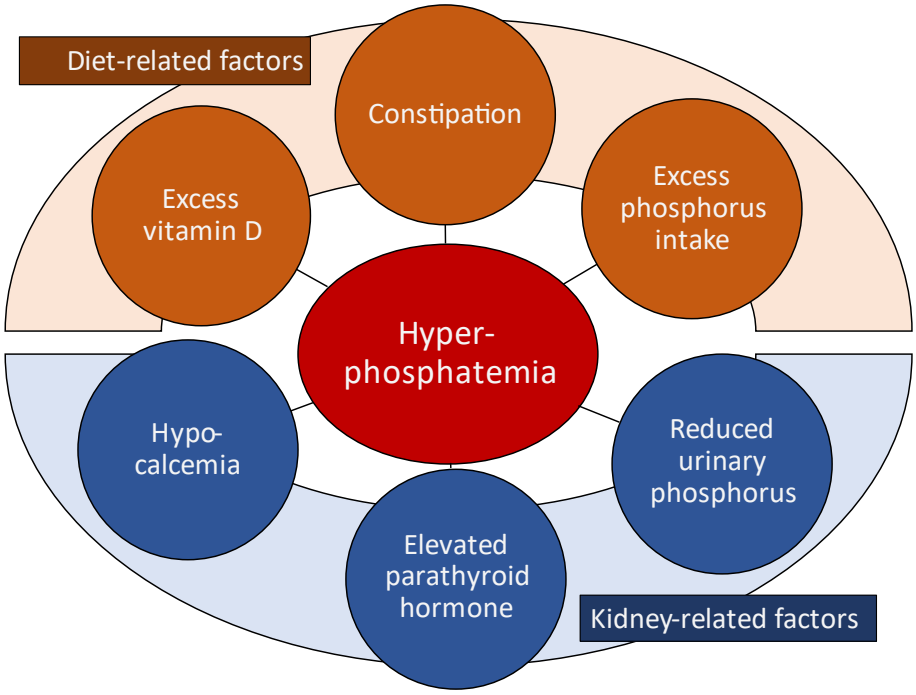


1.2.3 Pathophysiology of hyperphosphatemia in CKD

The kidneys play an important role in phosphorus balance. Phosphorus balance is maintained through several inter-related mechanisms. Kidneys regulate phosphate through renal thresholds which are equal to normal plasma concentrations.[6] In a well-functioning kidney, if dietary intake of phosphorus exceeds physiological requirements, excess amounts will be excreted in the urine. An important regulator of urinary phosphorus excretion is fibroblast growth factor (FGF)-23.[13] FGF-23 levels increase in response to elevated serum phosphate levels and increase phosphorus excretion in the urine though decreasing reabsorption in the proximal renal tubules.[13] In early stages of kidney disease, increases in FGF-23 are seen and help maintain normal serum phosphorus levels.[13] However, as kidney function declines, and the

number of nephrons that are available for FGF-23 declines, the ability of FGF-23 to maintain normal serum values declines.[13]

Figure 1.3: Factors contributing to hyperphosphatemia



The gut also plays a role in phosphorus excretion and reduced fecal output (constipation) related to low fibre diets may also be a factor. However, another factor involved in intestinal-related phosphate balance is the role of the kidneys in vitamin D activation. The kidneys are responsible for activation of vitamin D.[6] Low serum phosphate levels will stimulate vitamin D activation which stimulates increased intestinal phosphate absorption.[6] Of note, FGF-23 down-regulates vitamin D activation and thereby plays a role in decreasing intestinal phosphate absorption.[14] Low active vitamin D will stimulate the parathyroid hormone to free additional

calcium and phosphorus from the bone through bone resorption.[6] High phosphate levels decrease serum calcium levels through the affinity of calcium and phosphorus precipitating into salts.[6] In normal physiology this precipitation occurs into the bone, however in kidney disease, this may occur in the vascular system leading to the vascular calcification.[15,16] As such, any of these factors may contribute to the development of hyperphosphatemia (**Figure 1.3**), which impacts both bone[17] and cardiovascular health.[15]

1.2.3 Nutrition recommendations for CKD

Given the complex interaction of the kidney with mineral metabolism and hemostasis, it is not surprising that there are numerous ways nutrition therapy can modulate disease progression. In early stages of CKD, the main focus of nutrition therapy is reduction of risk factors for kidney function decline. For example, to manage hypertension, dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) diet that focuses on increasing plant foods consumption, or increased potassium intake are recommended.[18] Reduction in sodium intake is also recommended, in part related to the role that sodium plays in activation of the RAAS and its connection to blood pressure. If diabetes is the cause of kidney damage, nutrition therapy that improves glycemic control, either through modification of carbohydrate type and amount or recommending healthy diet patterns (such as the Mediterranean diet, vegetarian or DASH diets) may help delay the progression of kidney disease.[19] Reduction in protein intake is recommended to reduce dietary associated kidney burden by minimizing dietary acid load and waste urea products handled by the kidneys.[20] If the disease progresses, by stage 3 CKD additional nutrition recommendations may be indicated. As kidney function declines, there is an increased risk of hyperkalemia.[12] A cornerstone of therapy for hyperkalemia prevention and

management is dietary potassium restriction.[9,20,21] Dietary phosphorus restriction may also be indicated by stage 3 CKD if hyperphosphatemia develops.[9,17,20]

1.3 Food Processing.[1]

Canada is the second largest purchaser, by weight, of highly processed food per person per year.[3] Food processing changes the nutrient profile of foods.[2] Highly processed foods tend to be more energy dense, lower in fibre and higher in sodium.[3] Based on data from the 2015 Canadian Community Health Survey, most of the sodium in Canadian's diet comes from processed foods.[22] A main concern with excess sodium intake is its impact on blood pressure.[23] In 2012, Health Canada provided direction to the food industry to reduce sodium in processed food.[23] Potassium is considered a suitable sodium replacement as it conveys a similar "salty" taste in foods.[24] Potassium substitution for sodium may be particularly challenging for those living with CKD who need to restrict both potassium and sodium.

1.3.1 The Nova system for the classification of processed foods

One system that has been proposed to help classify foods based on level of processing is the Nova system. Nova uses four groups to describe how, how much and why a food item is processed.[3] The four groups are unprocessed or minimally processed, processed culinary ingredients, processed and ultra-processed.[3] **Table 1.1** summarizes the Nova groups.

Table 1.1: Summary of the Nova classification system. Adapted from Moubarac et al. [1]

Group	Description	Examples
1	Unprocessed or minimally processed – no additional substances are added to foods.	Fresh or frozen fruit, vegetables, and grains; Eggs; Milk; Fresh meat, seafood; Unsalted nuts and seeds

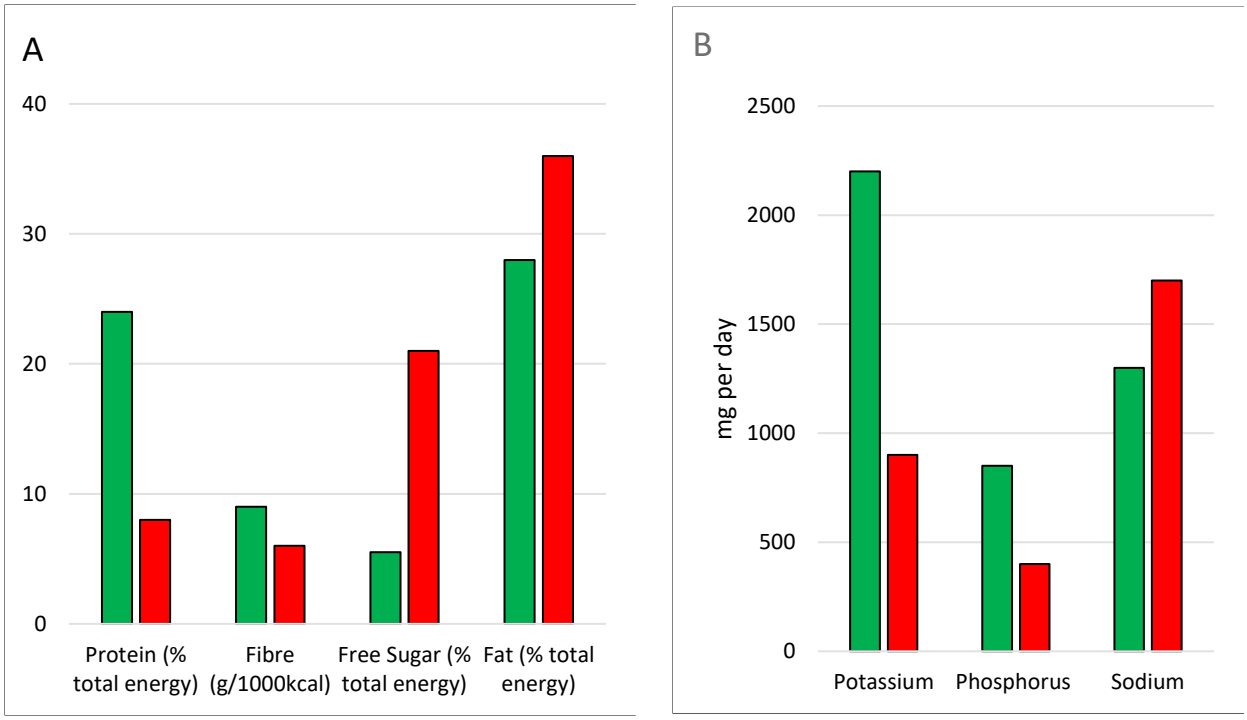
[1] Section 1.2 was adapted from a perspective in practice published by Picard, K., D. Mager, and C. Richard, *How Food Processing Impacts Hyperkalemia and Hyperphosphatemia Management in Chronic Kidney Disease.* Canadian Journal of Dietetic Practice and Research, 2020. **81**(3): p. 132-136. These were used with permission from the publisher.

2	Processed culinary ingredients – processing may include milling or grinding.	Plant oils; Animal fats (butter); Sugar; Salt; Flour
3	Processed foods – preservation methods may include canning or bottling. May add salt, sugar or oils.	Salted or smoked meat; Cheese; Bread; Canned vegetables or legumes in brine; whole fruits preserved in syrup.
4	Ultra-processed foods, foods made mostly from substances derived from foods and additives, with little Group 1 foods left intact	Bologna; Hot dogs; Breakfast cereals; Cake mixes; Sweetened breads and buns; Packaged soups and noodles

Ultra-processed foods tend to have higher energy density, more refined sugars, saturated fats and salt while being low in fibre. Their consumption is thought to increase the risk of obesity and other lifestyle-related chronic diseases.[25] Consumption of ultra-processed foods in Canada is increasing.[1] In 2014, Moubarac et al[1], analyzed data collected in the household food expenditure survey from Statistics Canada. They reported that in 1938, 71.3% of energy available from foods came from Group 1 and 2. By 2001, this number had decreased to 38.3%.[1] By 2001, Group 3 and 4 accounted for 61.7% of household energy availability, with 54.9% from Group 4 specifically.[1]

In 2017, data published from the Canadian Community Health Survey (2004-2005) illustrated how the fraction of the diet from Group 4 foods compared to the fraction of the diet from Group 1, 2 and 3 foods. The results are summarized in **Figure 1.4**.[3] As demonstrated in Figure 1.4, foods that are less processed tend to be higher in beneficial nutrients for the general population, such as protein, fibre, potassium and phosphorus while being lower in detrimental nutrients such as free sugars, fat and sodium.

Figure 1.4 More of the good, less of the bad - Average macro- and micronutrient intake reported in the Canadian diet (Canadian Community Health Survey 2004-2005) based on the NOVA classification system. Proportion of macronutrient (panel A) and micronutrient intake (panel B) coming from group 1, 2 and 3 in green and group 4 in red. Survey data was analyzed, in part, using the Canadian Nutrient File. Numbers as reported in Moubarac et al, 2017[3]



1.3.2 The impact of food processing on nutrition in CKD

Figure 1.4 shows that group 1, 2 and 3 foods contributed more potassium and phosphorus to the diet than Group 4 foods. However, dietary micronutrient calculations are done using nutrient databases, meaning that estimates as displayed in Figure 1.4, are only as reliable as the data that is used to calculate them. Product reformulation impacting the mineral content of food by necessity impacts the overall mineral content of the diet. This has particular concern for those with CKD because products that may have previously been low in potassium may become high.

In Canada, an important nutrient database is the Canadian in Nutrition File. In 2018, Parpia et al[26], analyzed 91 meat, fish and poultry products for sodium, potassium and phosphorus and compared the results to the Canadian Nutrient File. There were significant discrepancies between the analyzed amount and the Canadian Nutrient File. Reported variances was 30% less sodium, 40% more potassium and 20% more phosphorus in the analyzed food compared to the values reported in the Canadian Nutrient File.[26] The discrepancy may be related to the age of the

Canadian Nutrient File data, as over 60% was analyzed prior to 2000.[26] In one example the Canadian Nutrient File information for deli ham was from 1983, when compared to the 2018 Parpia et al[26] analysis the Canadian Nutrient File over-reported sodium by 302mg and under-reported potassium by 311mg.

In summary, consumption of processed food is increasing. The sodium content of this processed food is expected to decrease, with concurrent increases in potassium and phosphorus-based food additives. These changes are resulting in inaccuracies in nutrient reporting from important nutrient databases. For those living the CKD this change may be particularly problematic given their risk of hyperkalemia and hyperphosphatemia.

1.4 Dietary Potassium Restriction[2]

Current recommendations for dietary potassium intake mainly focus on restriction when hyperkalemia occurs, yet there is not consensus on the target dietary potassium intake for adults with CKD. The 2004 KDOQI (Kidney Disease Outcome Quality Initiative) guidelines recommend that patients with stage 3-5 CKD limit potassium to 2 to 4 grams per day.[27] In 2020, KDOQI updated the 2004 nutrition practice guidelines. The 2020 KDOQI guidelines recommend reducing potassium intake when hyperkalemia is present, though they do not provide a specific potassium intake target.[20] The 2010 Academy of Nutrition and Dietetics CKD guidelines recommend patients with stage 3-5 CKD who have hyperkalemia to limit their dietary potassium intake to less than 2.4 grams per day.[28] The 2013 Caring for Australians with Renal Impairment (CARI) guidelines do not stipulate a dietary potassium target, but recommend that patients with

[2] Section 1.3 was adapted from a systematic review published by Picard K, Barreto Silva MI, Mager DR, & Richard C (2020). Dietary Potassium Intake and Risk of Chronic Kidney Disease Progression in Predialysis Patients with Chronic Kidney Disease: A Systematic Review. Advances in Nutrition, Volume 11, Issue 4, July 2020, Pages 1002–1015, DOI: https://doi.org/10.1093/advances/nmaa027. These were used with permission from the publisher.

hyperkalemia lower their potassium intake with the assistance of a dietitian.[9] The 2015 Dietitians of Canada Practice Based Evidence in Nutrition (PEN) guideline recommends reducing dietary potassium intake to 2 grams per day when hyperkalemia is present.[21] In 2020, Kidney Disease Improving Global Outcomes (KDIGO) released executive conclusions on potassium management in the CKD population; they highlight the lack of evidence on potassium intake and CKD outcomes.[11] Furthermore, they concluded that routine potassium restriction to manage serum levels may prevent patients for the benefits of potassium rich foods.[11]

In summary, most guidelines recommend limiting potassium intake though target intake is not consistent and a lower limit for potassium intake is rarely specified. Additionally, despite consistent recommendations to limit potassium, guidelines do not provide explicit strategies or recommendations on which foods to restrict to implement a low potassium diet. For the most part, this step appears to be done by clinicians or health agencies who create patient teaching materials. Very little has been documented on how low potassium diet recommendations are translated into specific food recommendations, globally or in Canada.

1.4.1 The current state of low potassium diets in Canada[3]

To assess the current state of low potassium diets in Canada we investigated the specific food recommendations made in patient handouts or resources.[29] Twenty-one unique resources, published between 2014 and 2019 met our inclusion criteria and were included in this analysis. All resources recommended restricting fruits and vegetables. Recommendations to limit milk (to ½ cup to 1 cup per day) and other foods such as coffee, tea, or chocolate were advised in 14 of the 21 handouts. Plant-based protein (e.g. legumes, nuts, and seeds) restriction was advised in 13

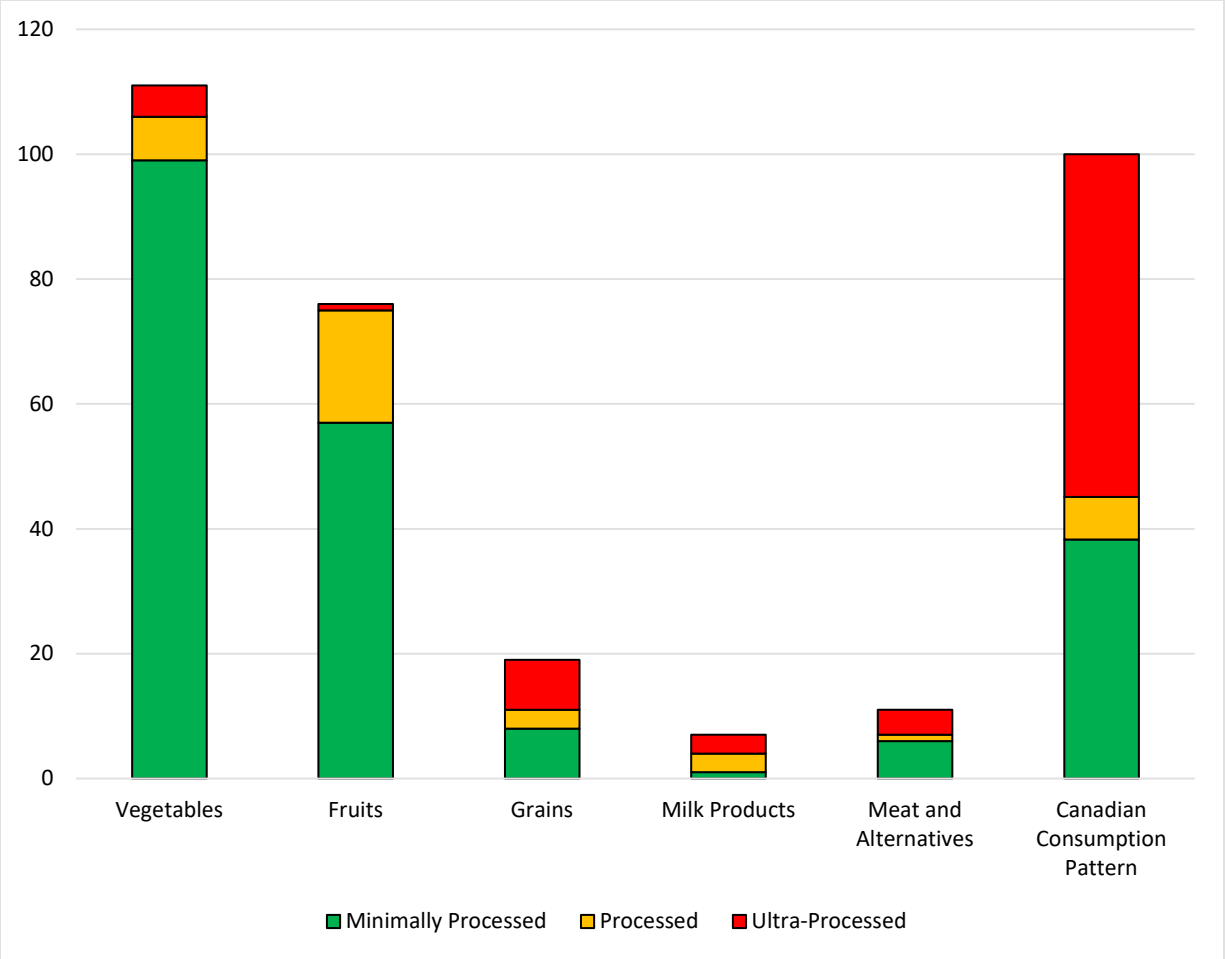
[3] Section 1.3.1 was adapted from a research brief published by Picard K, Griffiths M, Mager DR, Richard C (2020) Handouts for low-potassium diets disproportionately restrict fruits and vegetables. Journal of Renal Nutrition. DOI: https://doi.org/10.1053/j.jrn.2020.07.001.

of the 21 handouts. Whole grain (e.g. bran, granola, and whole grain bread) restriction was advised in 12 handouts. Two handouts mentioned animal-based protein as a source of high potassium foods. Eleven handouts recommend avoiding potassium-based salt-substitutes (i.e. half or light salt), and 6 handouts recommended avoiding potassium additives in other foods or reading labels to look for hidden potassium sources.

Two hundred and twenty-four different foods were listed to be either avoided or limited, including 111 vegetables, 76 fruits, 19 grain products, 7 dairy products, and 11 protein foods (**Figure 1.5**). Figure 1.5 shows that the target food restriction for low potassium diets is minimally processed foods. This contrasts with typical Canadian consumption patterns, where primary intake comes from processed and ultra-processed foods. Furthermore, early evidence is starting to suggest that potassium from minimally processed plant foods, where cell walls are intact is less bioavailable, than potassium from animal foods (which do not contain cell walls) or from potassium additives.[30]

Therefore, current practice for low potassium diet teaching is problematic for two reasons. First these recommendations are counter-intuitive, minimally processed tends to be higher in fiber, lower in sodium, contain less bioavailable potassium and likely should be encouraged. Second these recommendations may be ineffective, as these restrictions focus on the minority as opposed to the majority of foods consumed.

Figure 1.5 Number of different foods advised to be limited or avoided on a low-potassium diet. In the first 4 columns, the total number of different foods listed as high potassium (to be limited or avoided) based on low-potassium diet handouts organized by level of food processing. In the final column, the percent energy intake of Canadians in 2001 based on level of food processing as reported by Moubarac et al.[1] is shown. Determination for classification of minimally processed, processed, and ultra-processed foods as per the NOVA Food Classification System.[25]



1.4.2 Literature review of potassium and disease progression in CKD[4]

Given the universality of low potassium diet recommendations in chronic kidney disease, one would anticipate that clear evidence would link this practice to hard clinical outcomes, such as reduced disease progression, hyperkalemia rates and morality. However, to the best of our knowledge, there was no review reporting the findings of studies regarding restriction of potassium intake in CKD and its impact on delaying disease progression (measured as eGFR decline), improving hyperkalemia rates or reducing mortality. Therefore, we conducted a

[4] Section 1.3.2 was adapted from a systematic review published by Picard K, Barreto Silva MI, Mager DR, & Richard C (2020). Dietary Potassium Intake and Risk of Chronic Kidney Disease Progression in Predialysis Patients with Chronic Kidney Disease: A Systematic Review. Advances in Nutrition, Volume 11, Issue 4, July 2020, Pages 1002–1015, DOI: https://doi.org/10.1093/advances/nmaa027. These were used with permission from the publisher.

systematic review to understand how different amounts of potassium intake impact disease progression among those living with CKD. Secondary outcomes were to investigate how potassium intake impacts mortality and serum potassium concentrations or hyperkalemia rates in CKD.

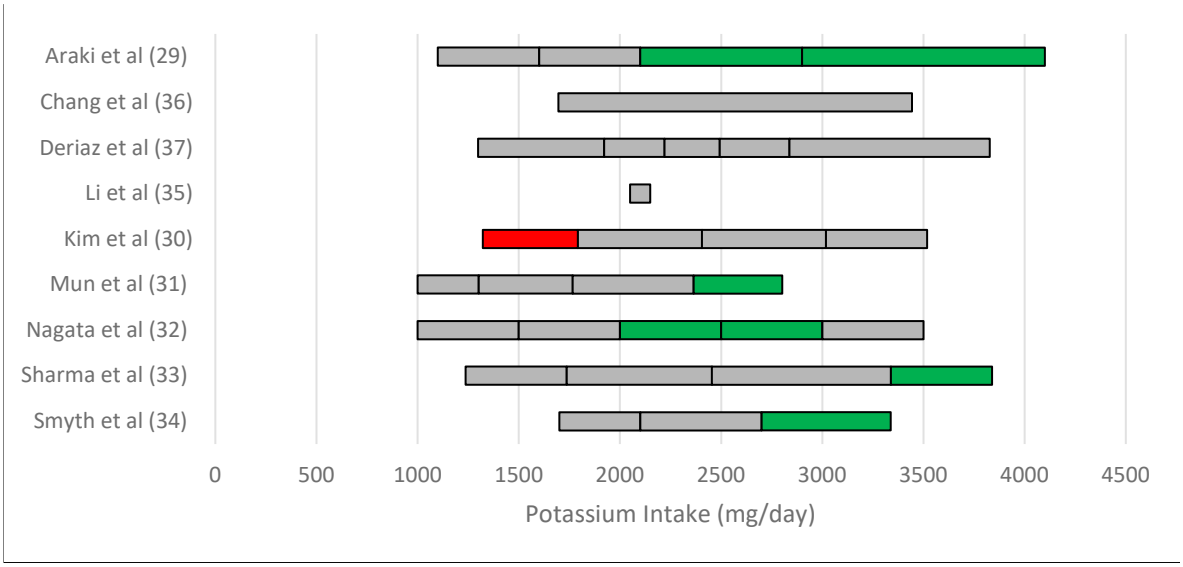
Initial screening identified 2404 studies, after removing duplicates, 1733 articles were eligible for title and abstract screening. Eighty-six full text articles were reviewed. Eleven studies met final inclusion criteria. We report outcomes separately for early (stage 1 and 2) CKD and late (stage 3-5) CKD.

1.4.2.1 Dietary potassium intake and disease progression in early CKD

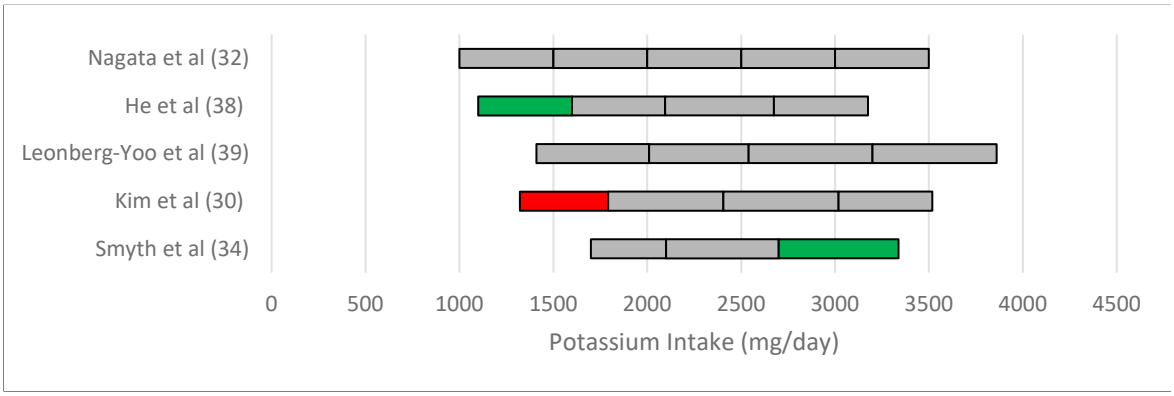
Nine studies were included patients with early CKD (stage 1 and 2) and reported on potassium intake and disease progression. Six reported either a protective effect of high dietary potassium intake on CKD progression or a harmful effect of low potassium intake on CKD progression[31-36]; three reported a neutral association[37-39] (**Figure 1.6A**). Dietary potassium intake in the highest quartile/quintile averaged above 2500 mg per day while the lowest quartile/quintile had an average potassium intake of about 1500 mg per day. For studies that reported a protective effect of dietary potassium on CKD progression when comparing the highest quartile vs lowest quartile, the hazard ratio (HR) ranged from 0.33 and 0.74.[31,33,34,36] Therefore, in stage 1-2 CKD, findings from this systematic review point toward an overall protective effect of higher potassium on CKD progression.

Figure 1.6: Results for papers investigating the impact of potassium intake on kidney function loss among participants with early (panel A) and late (panel B) stages of CKD. Green boxes denote potassium intake range associated with reduced risk of kidney function loss and red boxes denote potassium intake range associated with increased risk of kidney function loss.

A



B



1.4.2.2 Dietary potassium and disease progression in late stage CKD

Five studies included patients with late CKD (stage 3-5) and reported on potassium intake and disease progression. One study suggested high potassium intake may be harmful as those who consumed the lowest amount of potassium had the lowest risk of disease progression.[40] Conversely, two other studies suggested high potassium intake may be beneficial, with one study reporting that those with the lowest potassium intake had the highest risk of disease progression [32] and another study reporting that those who consumed the most potassium

had the lowest risk of disease progression.[35] Two studies reported no associated with potassium intake and disease progression.[34,41] Therefore, in stage 3-5 CKD, findings were mixed preventing a clear understanding of how potassium intake impacts disease progression.

1.4.2.3 Dietary potassium intake and mortality

Results for dietary potassium intake and all-cause mortality were either positive or neutral as presented in **Table 1.2**. Four studies investigated dietary potassium intake and mortality, reporting either a benefit of high potassium[31,34,41] or no association.[40] Of note, no studies reported a higher risk of mortality with increased potassium intake.

Table 1.2: Dietary Potassium Intake and Mortality

Author	Summary of Result	Statistics as provided by the article
Araki et al[31]	Higher potassium is beneficial. Highest quartile had lowest all-cause mortality.	HR (95% CI) 0.71 (0.56 to 0.90)
He et al[40]	Neutral. Not associated with all-cause mortality. 95% CI across all quartiles crossed 1.	HR (95% CI) Q4 vs Q1 0.89 (0.64 to 1.23)
Leonberg-Yoo et al[41]	Higher potassium is beneficial. All-cause mortality average follow up 19.2 (10.8-20.6 years); Lower quartiles higher risk for mortality	HR (95% CI) Q1 vs Q4 1.71 (1.23-2.38)
Nagata et al[34]	Moderate potassium is beneficial. Death - comparing reference category of <1.5gram to 2.0-2.5gram and 2.5-3 gram, lowest risk in higher quartiles	HR 0.36 (95% CI 0.19 to 0.70)

1.4.2.4 Dietary potassium intake and serum potassium levels or hyperkalemia rates

Regarding the relationship between dietary potassium intake and serum potassium levels or hyperkalemia events, four studies reported on this outcome. Studies unanimously reported no association between potassium intake and serum potassium or hyperkalemia rates. Smyth et al[36] reported a higher odds ratio for hyperkalemia with increased potassium intake, however the association became non-significant after adjusting for known risk factors (including age, sex, eGFR, urine albumin creatinine ratio, diabetes, RAASi, diuretic use, BMI, smoking and urine sodium excretion; OR1.16 (95% CI: 0.99–1.36)).

1.4.3 Dietary potassium restriction summary

Our literature and practice reviews highlight that low potassium diets disproportionately restrict minimally processed fruits and vegetables. This practice does not appear to be well supported in the literature, with evidence suggesting that higher potassium intake, especially in earlier stages of kidney disease, may help slow disease progression. Furthermore, evidence linking dietary potassium intake to serum potassium levels is lacking.

1.5 Dietary Phosphorus Restriction[5]

As kidney function declines, the ability to excrete excess phosphorus decreases.[20] As such, the 2020 KDOQI guidelines recommend modifying phosphorus intake to help achieve normal serum phosphorus levels.[20] KDOQI also encourages considering phosphorus source as it has been demonstrated that the phosphorus from animal sources has a higher bioavailability than phosphorus from plant sources.[42] Bioavailability of phosphorus from animal sources has been estimated to be 40 to 60% whereas plant sources has been estimated to be 20 to 50%.[20] Other sources of phosphorus come from processed foods with phosphorus additives. Phosphorus additives are considered highly bioavailable often estimated to be as high as 100%.[43] Specific directions regarding which foods to restrict to implement a low phosphorus diet are not provided in 2020 KDOQI guidelines. Food lists were also not provided in the previous 2000 KDOQI guidelines[44], the CARI[9] or the KDIGO guidelines.[17] Therefore, translation of nutrition practice guidelines into specific food recommendations is likely being conducted by clinicians or other health agencies.

[5] Sections 1.4 and 1.4.1 were adapted from a research paper published by Picard, K., Razcon-Echeagaray, A., Griffiths, M., Mager, D., & Richard, C. (2022). Currently available handouts for low phosphorus diets in chronic kidney disease continue to restrict plant proteins and minimally processed dairy products. Journal of Renal Nutrition. These were used with permission from the publisher.

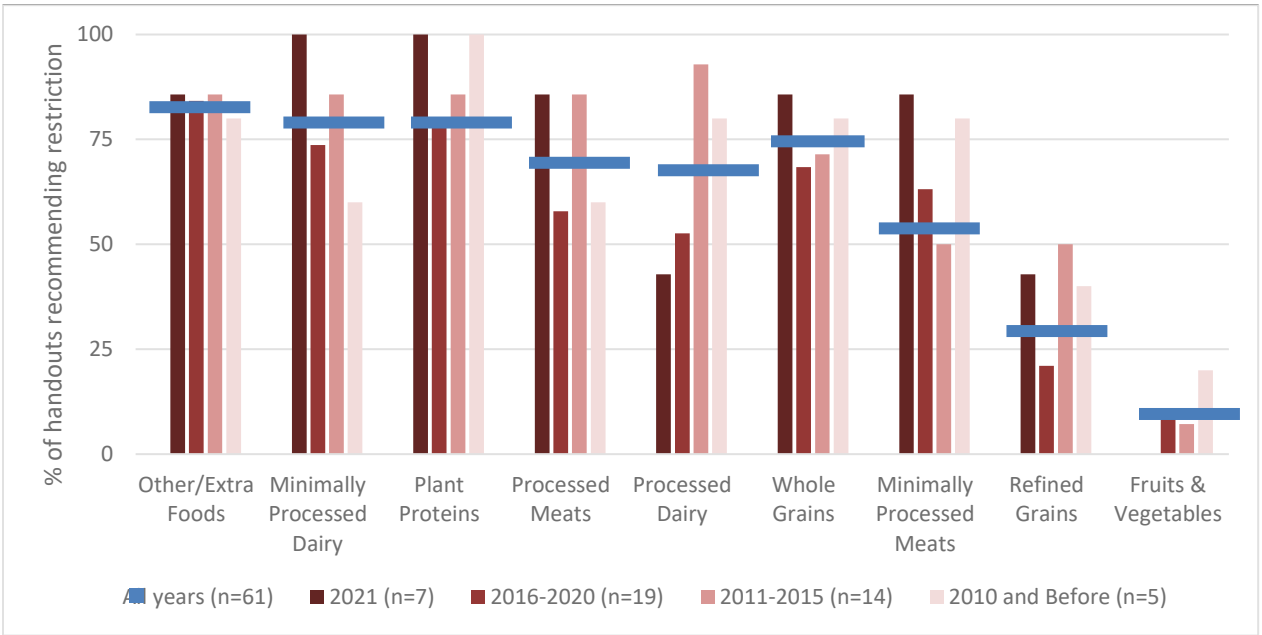
1.5.1 The current state of low phosphorus diets in Canada

To understand which foods are restricted on a low phosphorus diet, patient handouts were reviewed from renal agencies and health authorities across Canada. Sixty-one resources met inclusion criteria. Thirty-seven (60.7%) resources made recommendations about what foods to choose or listed low phosphorus food items. Thirty-nine (63.9%) resources mentioned phosphorus additives, 33 (54.0%) reviewed label reading for phosphorus additives and 22 (36.1%) mentioned that additives have higher bioavailability. The most commonly restricted food types were items with minimal nutrition value, with 83.6% of resources recommending a restriction of these types of foods (**Figure 1.7**). Items with minimal nutrition value encompass foods that would not fall into any of the traditional food groups from Canada's Food Guide.

All handouts released in 2021 mentioned restricting additives, compared to 20% of handouts created before 2010. Over 86% of handouts from 2021 also recommended restricting whole grains, while 100% recommended restricting minimally processed dairy products and plant proteins. The three most commonly restricted items were items with minimal nutrition value including cola, beer, hot chocolate, chocolates, and baking powder. The next most common food restrictions were plant proteins and minimally processed dairy products with 80% of resources recommending these types of restrictions. The least commonly restricted food items were fruits and vegetables, and refined grain products with 10% and 31% of resources, respectively.

Figure 1.7: Percent of handouts making specific food restriction for low phosphorus diets. Other/Extra foods are items with minimal nutrition value and do not belong to any of the traditional food groups of Canada's food guide. Plant protein restriction includes foods such as beans, lentils, legumes, nuts and seeds. Minimally processed dairy includes milk, yogurt and cheese. Processed meats include deli meats, prepared meats. Processed dairy includes ice cream, pudding. Minimally processed meats includes all beef, chicken, fish, pork, eggs. Refined grains - includes processed grain products such as boxed noodle with seasoning, baking mixes with

additives. As not all products included a publication date, these items are not represented in the by year restrictions but are captured in the All Years category.



Of all the restricted food items, 47% were considered ultra-processed while 32% were considered unprocessed or minimally processed. Of the recommended low phosphorus alternative food items, 39% were considered ultra-processed while 40% were considered unprocessed or minimally processed.

1.5.2 I impact of protein type on phosphorus intake and serum phosphate levels [6]

The impact of food processing and phosphate additives on total dietary phosphorus consumption and serum phosphate levels has been better elucidated than potassium additives, though it was noted that plant protein restriction remains a common practice to help lower phosphorus intake. Therefore, we reviewed the literature, with a specific aim of summarizing the

[6] Section 1.4.2 was adapted from a review published by Picard K, Mager DR, Richard C (2021) The impact of protein type on phosphorus and nutrition status in patients with chronic kidney disease: a critical review. Advances in Nutrition. DOI: http://doi.org.10.1093/advances/nmab062. These were used with permission from the publisher.

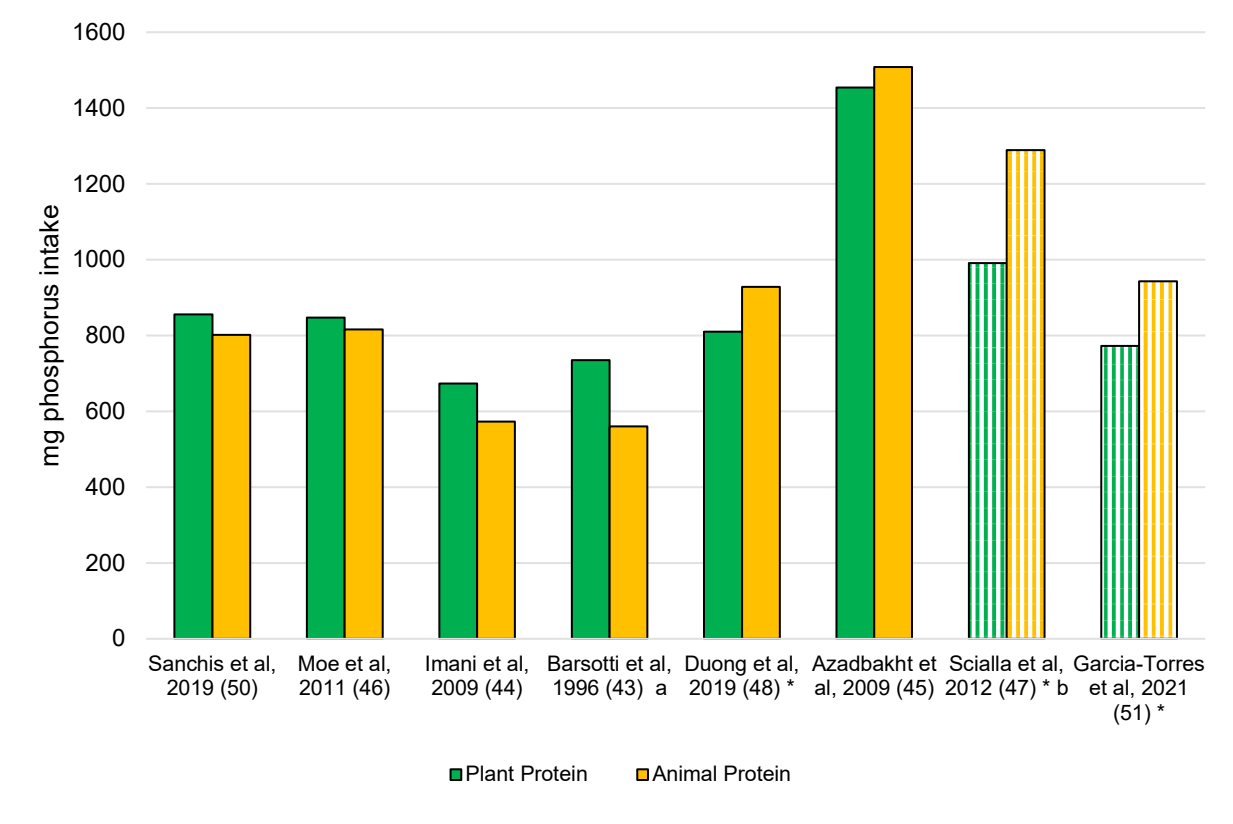
evidence on the impact of protein type (plant versus animal) on total dietary phosphorus intake and serum phosphorus concentrations. As a secondary outcome of interest, impacts on nutritional status (measured by albumin and body mass index (BMI)) and dietary intake (protein and energy intake) were also collected. Finally, health outcomes as reported by the included articles related to protein type were also summarized. The initial screen identified 971 articles, resulting in 22 full text reviews. Of these fifteen articles met inclusion criteria. All reference lists of included articles were screened and this yielded one more paper meeting inclusion criteria. Therefore, 16 articles were included, 11 reporting on diet outcomes, 15 on serum outcomes and 16 on nutrition outcomes.

1.5.2.1 The impact of plant vs animal protein on phosphorus intake

Ten articles reported on the impact of protein type on dietary phosphorus content. Of these, eight articles provided phosphorus intake for both plant-based diets (or vegetarian participants) and animal-based diets (or omnivorous participants) (**Figure 1.8**).[45-52] Figure 1.8 shows that higher plant protein intake was associated with either significantly lower intakes of phosphorus or equivalent intake.[45-49,52,53] The remaining two studies did not report on specific phosphorus content, but used a correlation analysis to explore the relationship of protein type on phosphorus intake.[54,55] Both of these studies reported a lower correlation between plant protein and phosphorus intake compared to animal protein and phosphorus intake ($r=0.586$ vs $r=0.674$ and $r=0.202$ vs $r=0.652$, respectively, all $p<0.05$). Therefore, the results of this review suggest that higher plant protein intake is associated with lower phosphorus intake.

Figure 1.8: Phosphorus intake by predominant dietary protein type (animal vs plant)
Figure Legend: Daily phosphorus intake by predominant dietary protein type. Green bars represent diets high in plant protein, yellow bars represent diets that were considered high in animal proteins or typical Western Diet patterns. Solid bars are intervention trials, patterned bars are observational trials. [a] Numbers for Barsotti et al were calculated using numbers provided in

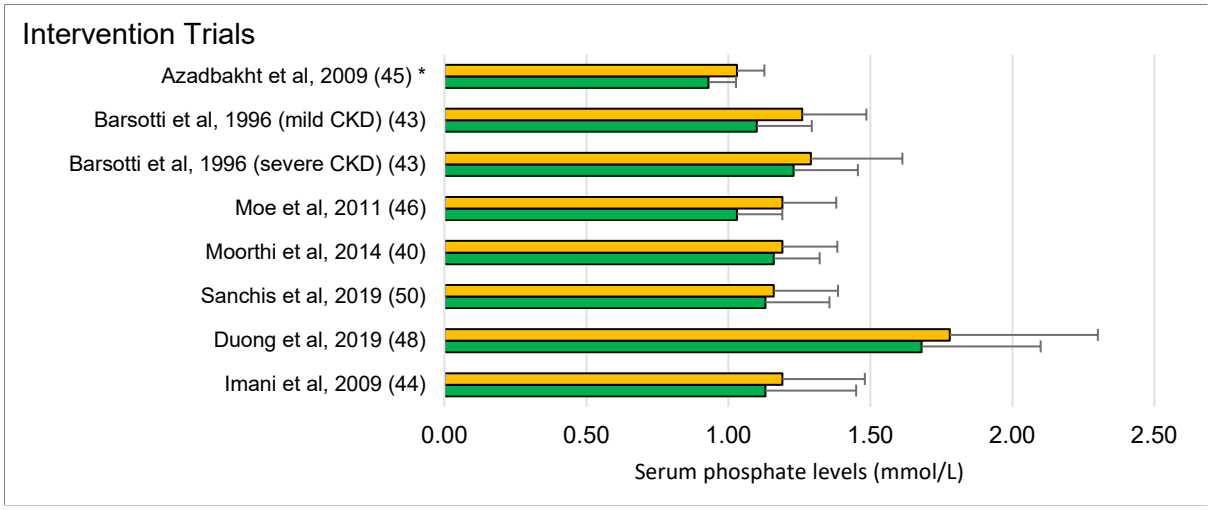
the article of phosphorus content per mg/kg of body weight and cited a 70kg person as typical subject. [b] For Scialla showing Q5 (highest plant protein intake) vs Q1 (lowest plant protein intake). * Denotes difference between protein type groups that achieved statistical significance ($p<0.05$)

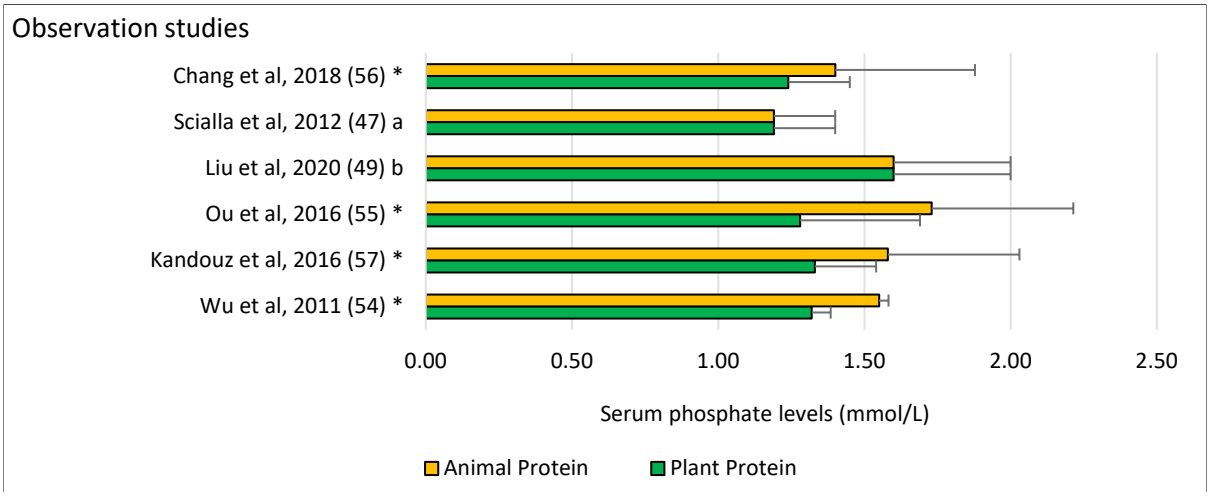


1.5.2.2 The impact of plant vs animal protein on serum phosphate levels

Fifteen studies reported on dietary plant versus animal protein and the impact on serum phosphate levels (**Figure 1.9**).[42,45-51,56-59] Six intervention trials demonstrated that diets providing slightly more phosphorus but equivalent protein from plant sources was associated with lower serum phosphate levels.[45-48,52] Of these, two were statistically significant.[47,48] Two uncontrolled intervention trials demonstrated that increased plant protein intake was associated

Figure 1.9: Serum phosphate levels by predominant dietary protein type (animal vs plant) in intervention trails and observation studies. [a] For Scialla et al showing results for Q5 (plant protein) vs Q1 (animal protein). [b] For Liu et al showing results for T1 (highest animal:plant protein ratio) vs T3 (lowest animal:plant protein ratio). * denotes difference between protein type groups that achieved statistical significance ($p<0.05$)





with lower serum phosphate levels compared to baseline, though these results were not statistically significant.[42,50] Four observational studies reported lower serum phosphate levels among those who self-identify as vegetarians compared to omnivores, all of which were statistically significant.[56-59] Two observational studies investigating the ratio of plant to animal protein consumption reported no difference in serum phosphate levels related to changes in protein type.[49,51] Two studies reported the correlation between plant protein intake and serum phosphorus levels only. Both reported weak associations ($r=0.0954$, $p=0.610$[54] and $r=0.194$, $p=0.053$[55]). Therefore, the results of this review suggest that higher plant protein intake is associated with lower serum phosphorus levels.

1.5.2.3 The impact of protein type on nutrition outcomes

All studies provided information on either nutritional adequacy of diets or clinical markers of nutritional status. Twelve articles provided information on nutritional adequacy of the diet (**Table 1.3**).[45-49,51-55,57,58] Nine observational studies provided one or more clinical markers of nutritional status.[49,51,53-59] There were two intervention trials long enough in duration (3-6 months) to evaluate the impact of protein type on nutritional status outcomes.[45,50] All other intervention trials were too short to provide information on how diet modification impacted clinical nutrition-status markers.

With regards to nutritional adequacy of diets, six interventions trials demonstrated that regardless of the primary protein type, equivalent protein and phosphorus, diets could be designed and meet the protein requirements for the predialysis population.[45-48,52] All observational studies reported that increased plant protein intake was associated with a statistically significant, lower total protein intake.[49,51,57,58] As protein recommendations for this population are made based on grams per kilogram body, this was also considered. Three observation studies either provided this information, or sufficient information such that it could be calculated. In the pre-dialysis population, one study reported that grams of protein intake to kilogram body weight met recommendations.[58] In the dialysis population, two additional studies reported that those who consumed more plant protein did not meet the g/kg protein target for this population[51,57], though in one of these studies, omnivores were also below target.[51] Three articles did not provide protein intake amounts intake but reported the correlation between protein type and total protein intake.[53-55] One article reported a stronger correlation between total protein intake and plant protein compared to total protein and animal protein ($r=0.627$ vs $r=0.574$, both $p<0.01$).[55] While the other two articles reported a stronger correlation between animal protein to

Table 1.3: Protein type and impact on protein intake

Study	Protein Type	Total Protein g/day	% Energy from Protein	Protein g/kg	Meeting protein target based on population[3]
Intervention Trials –predialysis participants					
Azadbakht et al, 2009[47]	Plant	54 ± 13	9%[1]	0.76[2]	Yes
	Animal	55 ± 18	9%[1]	0.83[2]	Yes
Barsotti et al, 1996[45]	Plant	NR	8%	0.70	Yes
	Animal	NR	7%	0.60	Yes
Duong et al, 2019[50]	Plant	NR	16.6% ± 3.4%	1.16 ± 0.32	Yes
	Animal	NR	17.7% ± 5.7%	1.33 ± 0.57	Yes
Imani et al, 2009[46]	Plant	43 ± 9	16% ± 3%	0.7 ± 0.2	Yes
	Animal	40 ± 15	16% ± 7%	0.6 ± 0.3	Yes
Moe et al, 2011[48]	Plant	78.9	15%[1]	Unable to assess	Unable to assess
	Animal	78	14.3%[1]		
Sanchis et al, 2019[52]	Plant	65.7	13.1%[1]	0.80	Yes
	Animal	66.1	13.2%[1]	0.80	Yes
Observation Studies – predialysis participants					
Chang et al, 2018[58]	Plant	46.3±14.9*	14.1%[1]	0.79±0.22*	Yes
	Animal	57.8±15.7	13.9%[1]	0.92±0.24	Yes
Scialla et al, 2012[49]	Plant	Not reported	13% ± 3%*	Not reported	Unable to assess
	Animal	Not reported	19% ± 4%	Not reported	
Observation Studies – dialysis participants					
Liu et al, 2020[51]	Plant	48.7 ± 13.9*	14.8%[1]	0.78 ± 0.24*	No
	Animal	54.7 ± 13.9	16.1%[1]	0.91 ± 0.24	No
Ou et al, 2016[57]	Plant	47.29±15.42*	13.1%[1]	0.94[2]	No
	Animal	60.57±21.88	14.5%[1]	1.08[2]	Yes

Articles that described protein intake related to primary protein type. Plant protein type refers to predominately plant or vegetarian type diet. Animal protein type refers to omnivorous or control diet.
[1] Calculated using information as provided by the authors. Calculated using the Atwater coefficient for protein. Formula used: g/day protein intake * 4 / total reported energy intake
[2] Calculated using the formula: protein (g/day) / body weight (kg)
[3] Protein target for predialysis 0.6-0.8g/kg; Protein target for dialysis 1.0-1.2g/kg
* Denotes statistical significant with $p<0.05$ when comparing plant to animal protein intake.

total protein than plant protein to total protein ($r=0.8997$ vs $r=0.5243$, both $p<0.05$)[54] and (0.761 vs 0.439, both $p<0.01$).[53]

With regards to clinical markers of nutritional status and protein type, there was no clear association between protein type and serum albumin levels. Only two studies reported

statistically significant differences. One study reported higher albumin levels among those who consumed more plant proteins[51], while the other reported higher albumin among those who consumed more animal proteins.[57]

1.5.3 Dietary phosphorus restriction summary

Our literature and practice reviews highlight that plant protein restriction remains a key strategy for phosphorus intake restriction and that this practice does not appear to be well supported in the literature. Evidence suggests diets high in plant proteins are not associated with increased phosphorus intake or higher serum phosphate levels.

1.6 Chapter Summary

Low potassium and phosphorus diets are recommended for adults living with CKD who experience hyperkalemia, hyperphosphatemia or both. Currently, minimally processed plant foods are the most commonly restricted foods for both of these diets. Despite this, there is not a clear link between dietary potassium intake and serum potassium levels. Nor is there a clear link between diets higher in plant proteins and higher phosphorus intake or serum phosphate levels. One potential explanation for this is the lower bioavailability of potassium and phosphorus from minimally processed plant foods contrasted with higher bioavailability from processed foods with additives. However, a significant challenge remains in understanding the prevalence of these additives in the food source, how these additives impact the mineral content of foods and which foods are more likely to contain them.

Chapter 2: Research Plan

2.1 Study Rationale

Kidneys play a fundamental role in maintaining electrolyte balance.[20] As such, CKD can increase the risk for hyperkalemia and hyperphosphatemia.[20] Hyperkalemia and hyperphosphatemia are both associated with increased morbidity and mortality [20], with increased morbidity potentially impacting health related quality of life. To manage hyperkalemia and/or hyperphosphatemia dietary restriction of potassium or phosphorus are recommended.[9,20,21] Potassium and/or phosphorus can be found in a variety of plant foods, including fruits, vegetables, nuts, legumes and whole grains. Animal foods including dairy and meat products are also sources. Potassium and phosphorus can be added to ultra-processed foods as additives.

Evidence suggests that different food sources of these minerals have different bioavailability, impacting electrolyte balance differently.[48,60] For both potassium and phosphorus, it appears that the bioavailablity of potassium and phosphorus is lower in minimally processed plant foods compared to animal products, which in turn is lower than the bioavailability of these minerals in processed foods. Furthermore, minimally processed foods are considered beneficial to health for the general population, whereas ultra-processed foods are not.[20,30]

In the general population, diets high in ultra-processed foods are typically associated with poor diet quality, however little is known in the CKD population about the impact of diet quality on health outcomes, particularly in reference to the management of electrolyte disturbances. One gap is that the potassium and phosphorus content of processed foods is not well described whereas the potassium and phosphorus content of minimally processed foods is. Another gap

remains as to whether high diet quality can modulate disease progression and prevent adverse outcomes for adults living with advanced CKD.

2.2 Objectives and Hypotheses

The primary aim of this research was to investigate the impact of food processing and diet quality on medical nutrition therapy for adults living with CKD. Specifically, this research sought to investigate the impact potassium and phosphorus additives have on mineral content of processed foods, health outcomes associated with poor diet quality and processed food consumption among the CKD population. Outcomes of interest include serum potassium and phosphorus levels, health related quality of life and hospitalizations. Three key objectives were identified for investigation.

Objective 1: Describe the state of medical nutrition therapy for dietary potassium restriction for adults living with CKD as it relates to:

A. Current clinical practice by investigating patient-facing resources (presented in Chapter 1)
B. The body of evidence on dietary potassium intake and its association with CKD progression and mortality (presented in Chapter 1)
C. The prevalence and the impact of potassium additives in the food source (presented in Chapter 3)
D. Explore the impact of sodium reformulation on potassium additive use in processed foods (presented in Chapter 3)

Hypothesis: 1) Restriction of dietary potassium intake in adults with CKD as per current nutritional guidelines will be associated with increased kidney disease progression and mortality

2) Potassium additives will be prevalent in processed foods and potassium additive use will increase potassium content. 3) Sodium reduced foods will be more likely to contain potassium additives than foods that have not undergone sodium reformulation.

Objective 2: Investigate medical nutrition therapy for dietary phosphorus restriction as it relates to:

A. Current clinical practice by investigating patient-facing resources (presented in Chapter 1)
B. The body of evidence examining the impact of plant versus animal protein sources on phosphorus intake and serum phosphorus levels (presented in Chapter 1)
C. The prevalence and the impact of phosphorus additives in the food source (presented in Chapter 3)
D. How protein source impacts outcomes (serum phosphate levels, hospitalizations, blood work) for adults living with CKD in Alberta (presented in Chapter 5)

Hypothesis: 1) Low phosphorus diets continue to routinely restrict minimally processed plant foods. 2) Phosphorus additives will be prevalent in the food source and their use will increase phosphorus content of foods 3) Plant protein foods will not be associated with worse patient outcomes but may be associated with improvements in diet quality.

Objective 3: Examine diet quality in CKD as it relates to:

A. Cardiometabolic risk factors, health related quality of life and mental health (presented in Chapter 4)
B. Which diet quality tool may be best suited to describe nutritional adequacy (presented in Chapter 4)

Hypothesis: Adults with CKD who have higher diet quality scores will have better cardio-metabolic risk factors, health related quality of life and serum potassium and phosphorus lab values.

2.3 Chapter Format

The above objectives and hypotheses were assessed in a series of different studies using a cross-sectional analysis and a longitudinal cohort study in adults with CKD (before and during dialysis) to assess clinical outcomes.[61-64] Investigations into food additive use were completed using the United States Department of Agriculture's (USDA) Branded Foods Product Database, a private public partnership to enable better transparency into nutrient composition of branded and private label foods.[65] These studies are organized into thesis chapters, which have been submitted and/or accepted for publication as individual manuscripts.

Chapter 3 reports on the examination of additives in the USDAs Branded Foods Product Database. [66] The relationship between potassium additive use and potassium content was examined which addresses Objective 1C. The relationship between sodium concentrations and sodium reformulation and potassium-based sodium substitutes was also examined and addressed Objective 1D.[67] Finally, the relationship between phosphorus additive use and phosphorus content was examined addressing Objective 2C.[68]

Chapter 4 reports on the impact of diet quality on cardiometabolic risk factors, health related quality of life and mental health in a longitudinal follow up of adults living with diabetes kidney disease, stages 1-5.[61-64] The relationship between Mediterranean Diet Scores and lipid profiles, the short form 36 (SF-36) to assess health related quality life and the major depressive index was examined. Objective 3A was addressed in this chapter. This chapter also reports on how three different diet quality tools relate to nutritional adequacy and potassium and

phosphorus intake in the longitudinal dataset.[69] The relationship between achieving the dietary reference intake for vitamins and minerals and the healthy eating index, healthy food diversity and Mediterranean diet scores was examined. Objective 3B was addressed in this chapter.

Chapter 5 reports on the impact of plant protein intake on health outcomes in a cross-sectional analysis of adults living with stage 4 and 5 CKD.[70] The relationships between protein source and serum potassium and phosphorus levels, diet quality and hospitalizations were examined. Objective 2D was addressed in this chapter.

Chapter 3: The prevalence of potassium and phosphorus additives in the food supply[7]

3.1 Abstract

Background: Ultra-processed foods can be a source of potassium and phosphorus additives. Intake of potassium additives can lead to excess potassium intake leading to hyperkalemia, excess intake of phosphorus additives may lead to hyperphosphatemia. How frequently potassium and phosphorus additives are found in the food supply and how additives change potassium and phosphorus content is not well documented.

Methods: Using the United States Department of Agriculture's Branded Foods Product Database (BFPD), ingredient lists were searched for "potassium" and "phos" to identify products containing potassium and phosphorus additives. A subset of the BFPD that provided potassium or phosphorus content was further analyzed for how mineral content differed between additive type and presence and food groups.

Results: The BFPD contains information on 239,089 products. Potassium additives were found in 35,102 (14.7%) contained potassium additives. 13,685 (5.7%) of products provided potassium content. 96.7% of these products provided probably accurate potassium content information, with 1,963 of these containing additives. Potassium additives were most commonly found in

[7] Chapter 3 includes a series of excerpts from three manuscripts, one published as "Picard K, Picard C, Mager DR, Richard C (2021). Potassium content of the American Food Supply and implications for the management of hyperkalemia in CKD: An analysis of the Branded Product Database. Seminars in Dialysis. DOI: https://doi.org/10.1111/sdi.13007", one submitted with revisions as "as "Picard K, Mager DR, Senior PA, Richard C. Potassium-based sodium substitutes and implications for those requiring concurrent sodium and potassium restricted diets. Journal of the Academy of Nutrition and Dietetics." and one submitted as "Section 3.2.3 is an excerpt from the manuscript submitted for publications as ""Picard K, Griffiths M, Senior PA, Mager DR, Richard C. Phosphorus additives and their impact on phosphorus content in foods – an analysis of the USDAs Branded Foods Product Database. Journal of Renal Nutrition."

dairy products, supplements and mixed foods (e.g. noodles with sauce) (at 37%, 34% and 28%, respectively). Potassium additives in mixed foods and vegetables and fruits were associated with 71% and 28% more potassium per serving, respectively ($p<0.01$). Potassium content increased by 1874mg (66%) when a one-day sample menu compared foods with and without additives. Reduced sodium products contained a higher proportion of products with potassium-based sodium substitutes than products without a sodium claim. Phosphorus additives were found in 74,601 (31.2%) of items in the BFPD. Phosphorus content information was available for 3,466 (1.45%) food items, of these 1791 (51.6%) contained additives. Surprisingly, median phosphorus content was lowest in products with only added lecithin than in products without any phosphorus additives (86 (54-200) vs 145 (77-351) mg per 100g, $p<0.01$), which was not different from products with phosphate salts (176 (101-276) mg per 100g, $p=0.22$) or products with both phosphate salts and lecithin (161 (99-285) mg per 100g, $p=1.00$). For all products phosphorus and potassium content were correlated, but the relationship was stronger for products which contained potassium phosphate additive when compared to products without potassium phosphates (rho = 0.81 vs 0.53, $p < 0.05$).

Conclusion: Potassium and phosphorus content of foods with and without additives is not well documented. Potassium and phosphorus additives are prevalent in the food system and may be associated with increased potassium and phosphorus content, respectively. However, more information is needed to better understand how different additives used in different foods change mineral content.

3.2 Introduction

North American's are the largest consumers of ultra-processed food worldwide.[71] Data from NHANES 2009-2014, showed that adult men consumed 56% of their energy from ultra-

processed foods, while women consumed 55%.[72] Processed foods contain less fibre and other beneficial nutrients.[3] Processed foods also contains more sodium and food additives than non-processed foods.[3] The concern with processed foods is particularly relevant for adults living with chronic kidney disease (CKD), as processed foods can be a source of potassium or phosphorus additives.[73]

3.2.1 Potassium

The 2020 Kidney Disease Improving Global Outcomes (KDIGO) position statement on potassium specifically note that potassium additives can be a significant source of hidden potassium.[11] The concern with potassium intake in this population is the potential risk of hyperkalemia [12], which is associated with an increased risk of mortality.[74] As such, nutrition practice guidelines for CKD typically recommend lowering potassium intake to either prevent or manage hyperkalemia.[9,20,21,44] Most resources for hyperkalemia management recommend restriction of minimally processed vegetables and fruits.[29] This intuitively makes sense, as many studies investigating dietary potassium source report vegetables and fruits as the primary source.[75-77] However, as minimally processed fruit and vegetable consumption decreases and consumption of processed food increases, the utility of this strategy has been called into question.[29,73] The 2020 KDIGO guideline suggest considering potassium additives when implementing low potassium diets.[11] However little is currently known about the frequency of potassium additive use or how their use changes potassium content.

3.2.2 The impact of sodium reformulation on potassium additive use

Potassium has been identified as an ideal candidate for sodium substitution in processed foods. A small study of meat, fish and poultry products reported that low sodium products with potassium additives contained more potassium than regular sodium products without potassium

additives. With regards to the CKD population, this study was important for two reasons. First, for many adults living with kidney disease, low sodium diets are recommended. Therefore, adults living with CKD may be more likely to look for low sodium products. Second, this was the among first studies to report on how sodium reformulation impacts potassium content, and highlighted the potential risk of consuming low sodium foods containing potassium-based sodium substitutes for adults requiring low potassium diets. However, a large-scale review of how sodium reformulation impacts potassium additive use and potassium content has not been previously reported.

3.2.3 Phosphorus

It was reported that phosphorus additives were found in as many as 44% of food items available for sale in the United States.[78] Currently, nutrition guidelines and educational materials do not differentiate between different types of phosphorus additives, as many handouts simply encourage patients to read ingredient lists for "phos" to identify if a product contains a phosphorus additive, such as monocalcium phosphate or phosphoric acid.[79] Lecithin is less often considered or mentioned on patient handouts as a phosphorus additive, however, several papers have listed it as a phosphorus containing additive[80-82], suggesting that lecithin contains as much as 2000mg phosphorus per 100g.[82] Lecithin, often added to food as an emulsifie, has previously been reported to be found in high amounts in ice creams, snacks, and cereal products.[80] Given that phosphorus additives are prevalent, there is likely benefit in understanding if different phosphorus additives impact phosphorus content in foods equally.

3.2.4 The Branded Foods Product Database

Gaps in information about the food source has been recognized, and in 2016 the United States Department of Agriculture (USDA) issued their first release of the Branded Foods Product

Database (BFPD).[65] This is the work of a private-public partnership enabling private industry to provide product-specific nutrition information which integrates with the USDA National Nutrient Database.[65] The goal of this work is to increase the ability of health care providers, researchers and consumers access the nutrient composition of foods available in the American food landscape.[65]

3.2.5 Chapter Aims

The aim of this chapter is to present data from the BFPD to describe potassium and phosphorus additives use. For potassium specifically, aims were to describe (1) how frequently foods report on potassium content and assess the accuracy of potassium reporting, (2) the proportion of foods that use potassium additives and which potassium additives are used, (3) the relationship between additive use and potassium content, (4) which foods contain potassium additives, and (5) investigate how sodium reformulation impacts potassium additive use. For phosphorus specifically, the aim was to explore phosphorus additive prevalence and type in the BFPD and explore how phosphorus additives impact phosphorus content in processed foods.

3.3 Methods

Using the 13 July 2018 Branded Foods Product Database files available on the USDA website (https://data.nal.usda.gov/dataset/usda-branded-food-products-database), first we collated the data to combine the food category number, product description, ingredient lists, mineral content for potassium, sodium and phosphorus (mg per 100g) and serving size.

3.3.1 How potassium and phosphorus additives were identified

3.3.1.1 Potassium Additives

A Microsoft excel (Redmond, WA, Microsoft Corp) text parsing algorithm was used to search ingredient lists for potassium using the following keywords: “potassium”, “potas*”,

"*sium". A macro was used to extract the potassium additive name. All items identified in the search had their ingredient lists audited manually and spelling errors were corrected accordingly (e.g. asesulfame potassium became acesulfame potassium).

3.3.1.2 Sodium reformulation and potassium additives

To determine if a product may have undergone sodium reformulation, we searched from products making a sodium content claim. To do this, a Microsoft excel (Redmond, WA, Microsoft Corp) text parsing algorithm was used to search for sodium or salt in the product description name. All products with sodium or salt in their name were individually reviewed to identify if the term sodium or salt was being used to make a sodium content claim or for another purpose (such as a flavour description, example salted caramel). Products identified as making a sodium content claim were grouped into sodium content claim categories using the Food and Drug Administration (FDA) Food Labeling Guide.[83] Only potassium chloride and potassium lactate were considered potassium-based sodium substitutes.

3.3.1.3 Phosphorus additives

Products were reviewed for the presence of phosphorus additives in the ingredients list using a text parsing algorithm with keywords of "phos" and "lecithin". Additives were grouped separately by lecithin and phosphorus additives. The first lecithin type and/or the first phosphorus-salt type were considered for correlation of the additive with nutrients of interest. Additives were grouped into their primary phosphorus-salt (e.g. calcium, potassium, sodium) with prefixes and suffixes (e.g. mono-, di-, tri-, or poly-) not considered.

3.3.2 The impact of additives on mineral content

Mineral content information for potassium, phosphorus and sodium was not available for all products. For products which provide potassium content, a subset analysis was completed.

Using the product description and ingredient list, foods were divided into nine food groups (beverages, condiments, dairy, grains, meat/fish/poultry and alternatives, mixed foods, snacks, supplements or vegetables and fruit). Within each food group, foods were further categorized in subcategories with the goal of grouping foods that would have a similar amount of naturally occurring potassium and/or phosphorus contents, depending on the analysis. Level of food processing, using Nova, was also considered in the grouping, with minimally or unprocessed foods being categorized into different groups than ultra-processed foods (e.g. minimally grains vs processed grains).[84]

3.3.2.2 Sodium content and reformulation impacts potassium additive content

Products from the Branded Foods Product Database making a sodium content claim in the product description were explored. To determine if a product made a sodium content claim, a Microsoft excel (Redmond, WA, Microsoft Corp) text parsing algorithm was used to search for sodium or salt in the product description name. Products identified as making a sodium content claim were grouped into sodium content claim categories using the Food and Drug Administration (FDA) Food Labeling Guide.[83] The sodium content claims were: sodium free (less than 5mg of sodium), very low sodium (between 5-35mg of sodium), low sodium (between 36-140mg), reduced sodium (25% less sodium than regular products), lightly salted (50% less sodium than regular products), and unsalted (no salt added during processing).[85] Potassium-based sodium substitute occurrence was tabulated by sodium content claim category.

Two documents were used to classify foods into sodium categories. For products with less than 140mg of sodium, the FDA Food Labeling Guide[83] was used, which categorizes sodium concentration into three groups: less than 5mg, between 5mg and 35mg and between 36mg and 140mg. As per the Food Labeling Guide, the sodium concentration used to assign a sodium

category is based on either the product serving or per 100g, depending on the product.[83] For products with small serving sizes (at or below 30g), the sodium concentration per 100g is used to determine the appropriate sodium category of the product.[83] For products with larger serving sizes (above 30g), the serving size is used to determine the appropriate sodium category.[83] For products with sodium concentration above 140mg, the FDA Guidance for Industry: Voluntary Sodium Reduction Goals document was used to classify foods as at or below sodium reduction targets or above sodium reduction targets.[86] The Voluntary Sodium Reduction document emphasizes gradual sodium reduction among top selling products, acknowledging technical limitations of sodium reformulation. Current targets recommend reductions of 2-33% and are product specific.[86] The sodium and potassium concentration of products were investigated based on small or large serving size and sodium category (less 5 mg, 5-35mg, 36-140mg, above 140mg but below sodium reduction target, above 140mg but above sodium reduction target) and whether or not the product contained a potassium-based sodium substitute.

3.3.3 Menu analysis of foods with and without potassium additives

To understand the potential impact potassium additives could have on daily intake, a one-day sample menu was developed based on a similar study that examined the impact of phosphorus additives on phosphorus content in the American food supply.[78] Products were selected from the subset Branded Product Database. Comparable items and serving sizes that did and did not contain potassium additives were used, whenever possible.

3.3.4 Statistical Analysis

Statistical analysis was performed using IBM SPSS statistics 25 (Armonk, NY, IBM Corp.) all testing was two-tailed and a predetermined significance level of 0.05 was set.

In the potassium analysis, descriptive statistics (percentages) were used to describe the proportion of foods reporting potassium content and containing a potassium additive, means and standard deviations were used to describe the potassium content by food group and category. Bootstrapping was preformed to generate the 95% confidence intervals using 1000 cases. Independent sample t-testing was used to assess the differences between foods with and without additives. ANOVA with Games-Howell post hoc testing was used to test for significance in differences of potassium content by potassium additive in uneven sized samples. As several products contained several potassium additives, we compared potassium content based on the first additive type, as ingredients lists are structured by decreasing ingredient content.

For the sodium analysis, sodium content claim and the presence or absence of a potassium-based sodium substitute were treated as categorical variables and products with 5 or less and more than 5 ingredients were treated as categorical variables. A chi-square test was used to test the proportion of products with and without a sodium content claim and with and without potassium-based sodium substitutes and products with more than 5 ingredients (considered ultra-processed) among products with and without potassium-based sodium substitute. To test the hypothesis that one sodium content claim had a higher prevalence of potassium-based sodium substitutes, column proportions was tested using a z-test. P-values for this test were adjusted using the Bonferroni method as multiple comparisons were made between each of the sodium content claims. Number of ingredients, serving size, potassium and sodium concentrations were treated as continuous variables. The normality of these variables within each of the sodium categories were explored using histograms and the Shapiro-Wilk test. A p-value of <0.05 indicated that data was not normally distributed. Median and interquartile range were used for non-normally distributed data. Non-parametric independent samples Mann-

Whitney U-test was completed to assess the differences in number of ingredients, serving size, potassium and sodium concentrations between the different sodium categories which did and did not contain potassium-based sodium substitutes. For all analyses, an alpha of <0.05 was considered statistically significant.

For the phosphorus analysis, the presence of a phosphorus additive was considered a categorical variable, and four groups of phosphorus additive type were identified: phosphorus-salts only, lecithin only, both lecithin and phosphorus or no additives. Mineral content of phosphorus, calcium, potassium, sodium, and iron were considered continuous variables. The normalcy of mineral content within each group was tested using histograms and the Shapiro-Wilk test. A p-value of <0.05 indicated that data significantly deviated from a normal distribution.

To explore the prevalence of additives among food categories, z-testing for columns proportions was performed. To test the difference in phosphorus content (mg per 100g) between the four additive categories, Kruskal-Wallis non-parametric testing was used. P-values for these tests were adjusted using the Bonferroni method as multiple comparisons were made between each of the phosphorus additive categories, with a cumulative predetermined alpha of <0.05.

To test how phosphate salts impact phosphorus content between processed foods, a Mann-Whitney U-test was used. Mann-Whitney testing was also used to test the differences in phosphorus and mineral (calcium, potassium, sodium and iron) content between products with and without phosphorus salts containing the target mineral (calcium, potassium, sodium and iron). Spearman's rho correlation testing was used to explore how mineral content of iron,

calcium, potassium and sodium was correlated with phosphorus content when products contained that specific minerals-phosphate salt. Rho values above 0.5 were considered strongly correlated.

3.4 Results

The Branded Foods Product Database provided an ingredient list for 239,089 products (**Figure 3.1**), 14.7% contained potassium additives and 31.2% contained phosphorus additives. Three sub-analyses were completed.

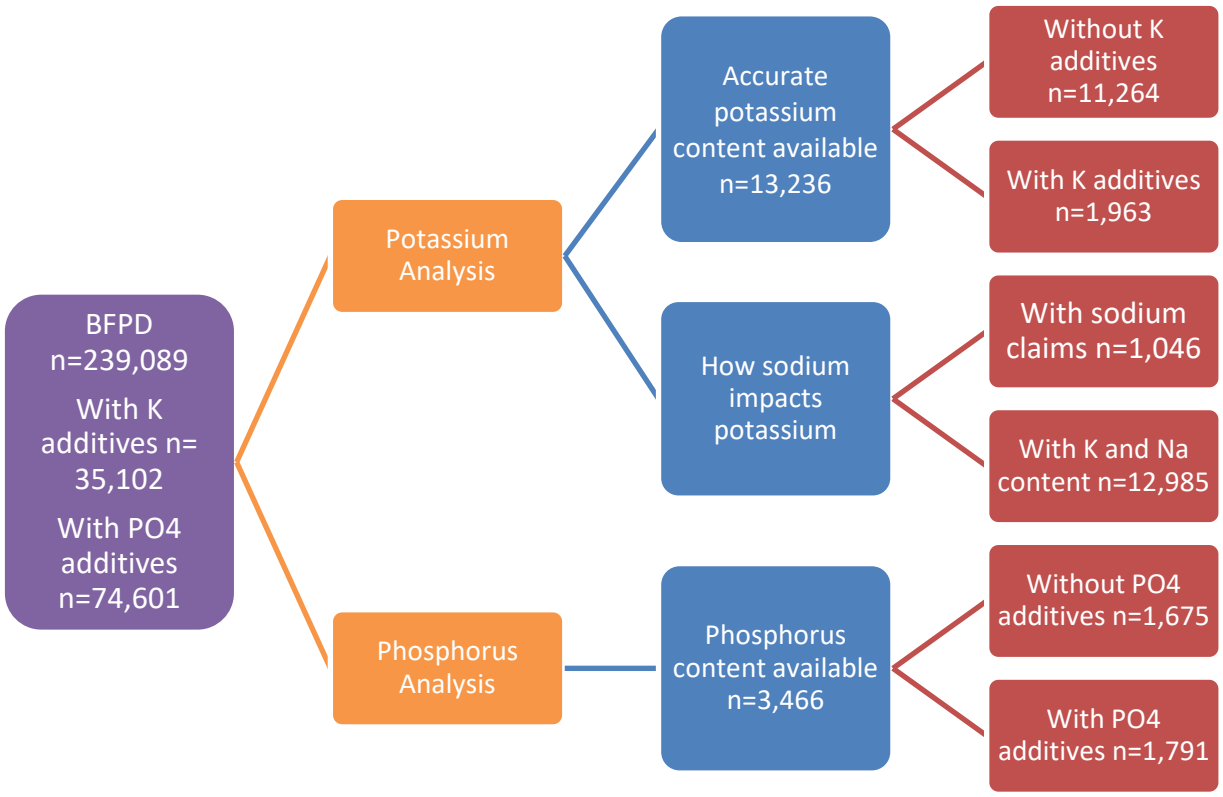


Figure 3.1: The USDA Branded Foods Product Database (BFPD) was reviewed for the presence of potassium (K) and phosphorus (PO4) additives. For products that reported on potassium content, made a sodium content claim, or reported on phosphorus, subset analyses were completed.

3.4.1 Potassium Additives

The most common additives were potassium sorbate, acesulfame potassium, potassium phosphates and potassium chloride (**Table 3.1)**. 14.8% of products providing potassium content contained potassium additives.

Table 3.1: The type of potassium additives found in the entire branded foods product database and the subset of the branded foods product database which provided potassium content information.

	Entire BFPD, n (%)	Subset BFPD, n (%)
Potassium Sorbate	19,483 (45.9%)	819 (33.4%)
Acesulfame Potassium	4,135 (9.6%)	312 (12.8%)
Potassium Phosphates	4,135 (9.6%)	354 (14.5%)
Potassium Chloride	3,954 (9.3%)	380 (15.6%)
Potassium Citrate	2,613 (6.2%)	223 (9.1%)
Potassium Benzoate	2,257 (5.3%)	87 (3.6%)
Potassium Lactate	2,046 (4.8%)	54 (2.2%)
Potassium Iodate/Iodide/Iodine	1,551 (3.7%)	142 (5.8%)
Potassium Bicarbonate/Carbonate	906 (2.1%)	46 (1.9%)
Potassium Sulfites[a]	427 (1.0%)	10 (0.4%)
Potassium Bromate	330 (0.8%)	1 (<0.1%)
Potassium Acetate	230 (0.5%)	0 (0.0%)
Potassium Hydroxide/Oxides	146 (0.3%)	2 (0.1%)
Unspecified or Other[b]	132 (0.3%)	4 (0.2%)
Potassium Acid Tartrate/Bitartrate	89 (0.2%)	2 (0.1%)
All Additives	42,434 potassium additives in 35,102 products	2,438 potassium additives in 1,963 products

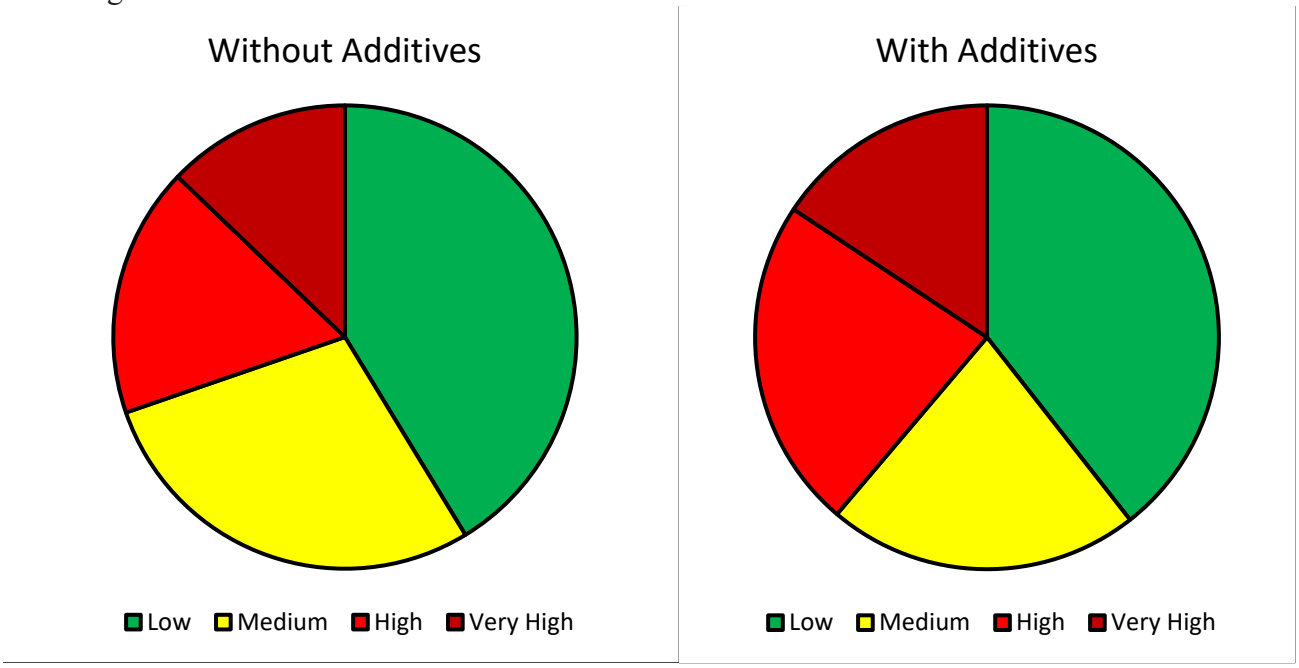
Foot Note: BFPD – Branded Foods Product Database. N describes the number of times the additive was found in the database. To understand how often the specific type of additive is used, the percent was calculated by dividing the number of occurrences of the specific additive/the sum of all potassium additives used. [a]Sulfites – includes sulfates, sulphites, sulphates, with or with meta- and bi- prefixes as the case may be. [b]Unspecified or Other in entire Branded Product Database (n in subset database provided when n>0): Aluminum Potassium Silicate (n=5), Ferrocyanide (n=1), Fluoride (n=1, in subset n=1), Gluconate (n=4), Glutamate (n=10), Guanylate (n=1, in subset n=1), Isonate (n=1), Nitrate or Nitrite (n=66), Sodium (n=4), Starch (n=2) and Unspecified (n=37, in subset n=2).

3.4.1.1 How much potassium is in food and how potassium additives impact potassium content

The mean potassium content for all items was 298mg ± 989mg per 100g of food. The bootstrapped 95% confidence interval was 283-316mg. For foods not containing a potassium additive, the mean potassium content was 277mg ± 306mg per 100g. The bootstrapped 95%

confidence interval was 272-283mg. For foods containing a potassium additive, the mean potassium content was 416mg ± 2457mg per 100g. The bootstrapped 95% confidence interval was 311-530. The foods highest in potassium differed depending on the unit of measure (i.e. per 100g vs per serving) (**Tables 3.2a and 3.2b**). 30% of food items without potassium additives could be considered as having a high or very high potassium content per serving, while 39% of foods with food additives could be considered high or very high (**Figure 3.2**).

Figure 3.2: Products in the subset Branded Product Database with and without potassium additives that could be considered either low, medium, high or very high in potassium mg per serving



Footnote: Additives – refers to potassium-based additives specifically. Low cut-off less than 100mg potassium per serving. Medium cut-offs 100-200mg potassium per serving. High cut-offs 200-350mg potassium per serving. Very high cut-offs above 350mg potassium per serving. Serving size as provided in the subset BFPD.

Table 3.2a: Top ten potassium foods by mg per100g

Ranking	Food Group	Food Category	mg/100g	Additive
1 (9 Items)	Condiments	Potassium-based salt substitutes	21000-49286	Potassium Chloride
2 (3 Items)	Beverage	Coconut Drink Mixes	5285-8750	Potassium Phosphate
3	Beverage	Electrolyte Drink	5285	Potassium Chloride
4	Beverage	White Tea	4150	No additive
5	Condiments	Spice and Seed Mixed Seasoning	4000	No additive
6 (2 Items)	Supplements	Powdered Beets and Black Cherries	3200	No additive
7	Meat & Alternatives	Concentrated Beef Broth	3083	No additive
8 (3 Items)	Sugars and Sweeteners	Blackstrap Molasses	2857-3000	No additive
9	Beverages	Spice Cider Drink Mix	2875	Potassium Citrate
10	Baking Ingredients	Cacao powder	2800	No Additive

Table 3.2b: Top ten potassium foods per serving size

Ranking	Food Group	Food Category	Potassium (mg/ser)	Additives
1	Mixed	Tomato, Squash and Chicken Meal Kit	1670	No Additive
2	Mixed	Ham and Cheddar Potatoes	1369	Potassium Chloride
3	Meat & Alternatives	Legume Based Pasta (3 products)	1263-1334	No Additive
4	Mixed	Fried Beef Steak and potatoes with Gravy	1330	Potassium Chloride
5	Meat & Alternatives	Turkey Deli Meat	1328	Potassium Chloride & Potassium Phosphate
6	Seasoning	Sweet Tamarind	1190	No Additive
7	Meat & Alternatives	Prepared Black Beans	1190	No Additive
8 (3 Items)	Mixed	Turkey Chili with Beans	1151	No Additive
9	Beverages	Chocolate Coconut Water (2 products)	1130	No Additive
10	Mixed	Cheese Ravioli in Tomato Sauce	1129	No Additive

Footnote: serving size as provided by the BFPD.

Different potassium additives impacted potassium content in foods differently. Products with potassium chloride, potassium citrate and potassium lactate contained 107%, 37% and 76% more potassium per serving, respectively (all $p<0.05$). Products with potassium phosphates and potassium lactate contained 63% and 105% more potassium per 100g, respectively (all $p<0.05$). Products with acesulfame potassium, potassium benzoate and potassium iodates/iodides were all associated with lower amounts of potassium per 100g and per serving than products without potassium additives. The presence of potassium carbonates or other potassium additives did not impact the potassium content in food products. Potassium sorbate was associated with reduced potassium content when considered per 100g, but this association became neutral when the potassium content per serving was considered.

The presence of potassium additives in mixed foods and vegetables and fruits was associated with more potassium per 100g and per serving compared to when additives were not present. The presence of additives in beverages was associated with greater potassium content per 100g but lower potassium per serving. In contrast, the presence of additives in grain products was associated with lower potassium content per 100g but greater potassium per serving. The presence of additives in condiments, meat, fish, poultry and alternatives, snacks and supplements were all associated with lower potassium contents per 100g but there was no statistically significant difference per serving.

A one-day sample 2000kcal menu using foods predominantly with vs without potassium additives found that in the additive free menu the potassium content was 2842mg of potassium (**Table 3.3**). In the food additive menu the potassium content was 4716mg, an increase of 1874mg (65.9%).

Table 3.3: Sample one day menu of foods with and without potassium additives.

With Additives	K (mg)	Additive Type	Without Additives	K (mg)	Difference (mg)
Breakfast					
Toasted Oats, Whole Grain Toasted Oats Cereal, 30g	200	Potassium Chloride	Organic toasted Oat Cereal, 28g	110	90
Almond Milk, 240g	250	Dipotassium Phosphate	Almond Milk, 240g	74	176
Split Top White Bread, 31g	25	Potassium Iodate	Enriched Premium White, 31g	25	0
Spreadable Butter, 14g	0	n/a	Spreadable butter, 14g	0	0
Creamy Chilled Coffee, 300g	570	Potassium Carbonate	Organic Cold Brew Coffee with Milk, 300g	276	294
Lunch					
Ham Sandwich			Ham Sandwich		0
100% WW Bread, 72g	160	Potassium Iodate	Market Basket, 100% Whole Wheat, 86g	110	50
Meijer Cooked Ham, 56g	390	Potassium Lactate	Everyday Value, Organic Black Forest Ham, 56g	190	200
Mayonnaise, 13g	0	n/a	Mayonnaise, 13g	0	0
Popcorn, 33g	190	Potassium Chloride	Popcorn, 28g	77	113
Kosher Dill Spears, 28g	120	Potassium Chloride	Organic Polish Dill Pickles, 28g	20	100
Citrus Salad in Light Syrup, 126g	150	Potassium Sorbate	Tropical Fruit Salad, 122g	150	0
Low sodium, 100% vegetable Juice, 240g	931	Potassium Chloride	Vegetable Juice Blend, 240g	691	240
Dinner					
Original Smoked Sausage Links, 76g	510	Potassium Lactate	Premium Sausage, 76g	271	239
Buttery Homestyle Mashed Potatoes, 28g	360	Dipotassium Phosphate	Mashed Potato Granules, 25g	170	190
Cut Corn, 85g	200	n/a	Cut Corn, 85g	200	0
Lowfat Yogurt, 170g	280	Potassium Sorbate	Lowfat Yogurt, 170g	281	1
Swiss Miss, Hot Cocoa Mix, 16g	380	Dipotassium Phosphate	Organic Drinking Chocolate, 15g	197	183
Total	4716			2842	1874

Footnote: Similar foods with and without potassium additives are compared in a sample one-day 2000kcal menu using products and potassium content as provided by the subset Branded Product Database. For products showing n/a in the Additive Type column this denotes there was not a comparable product that had potassium additives in it.

3.4.1.2 Which Foods Contain Potassium Additives

All food groups had food items with potassium additives (**Figure 3.3, Table 3.4**). Most food categories (88 out of 110) contained potassium additives, however 22 did not. Of the additives likely to increase potassium content, potassium chloride was found in 59 different food categories, potassium citrate in 18, potassium lactate in 8 and potassium phosphate in 36 food categories. There was an insufficient quantity of food products within each food category to complete statistical analysis.

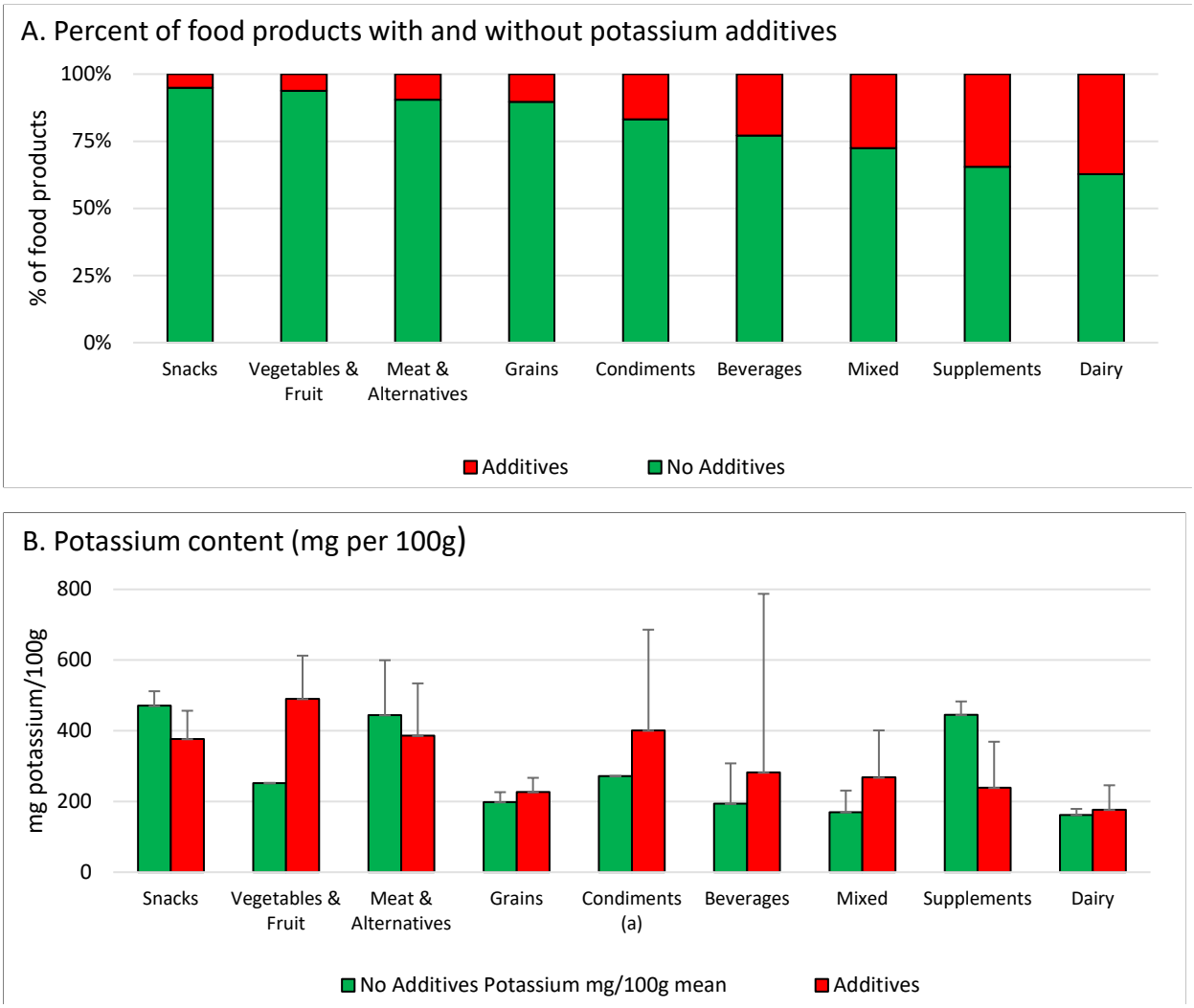


Figure 3.3: Portion of additives (A) and potassium content (mg/100g) (B) in foods with and without additives in different food groups. (a) displaying potassium/ 10g to allow for comparison using standardized unit to prevent distortion on by-axis amounts. Multiply values by 10 for amounts per 100g.

Table 3.4: The mean potassium content of food groups when potassium additives are and are not present

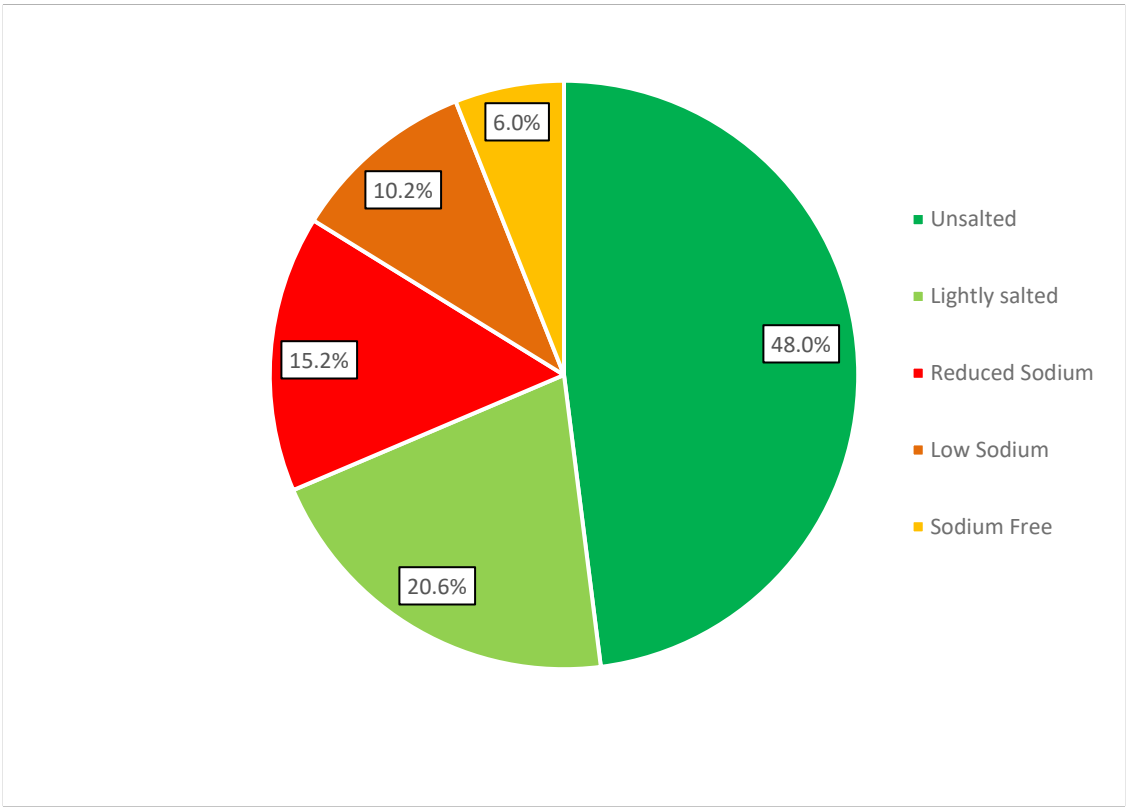
Food Group	Additives	N	Potassium mg/100g	Difference (mg/100g)	p-value	Potassium mg/serving	Difference	p-value
Beverages	No	1234	194 ± 308	89	0.04	280 ± 215	-157	<0.01
	Yes	367	282 ± 788			123 ± 171		
Condiments	No	390	272 ± 215	3738	0.01	63 ± 120	16	0.37
	Yes	79	4010 ± 11584			79 ± 146		
Dairy	No	797	162 ± 179	15	0.06	225 ± 172	-6	0.44
	Yes	474	177 ± 108			219 ± 108		
Grains	No	3448	198 ± 171	29	<0.01	81 ± 78	31	0.01
	Yes	397	227 ± 187			112 ± 102		
Meat & Alternatives	No	1329	445 ± 290	-59	0.01	217 ± 128	26	0.06
	Yes	140	386 ± 238			243 ± 159		
Mixed	No	454	170 ± 109	98	<0.01	278 ± 211	198	<0.01
	Yes	173	268 ± 135			476 ± 240		
Snacks	No	1560	471 ± 430	-94	0.01	166 ± 130	-3	0.85
	Yes	84	377 ± 297			164 ± 125		
Supplements	No	245	445 ± 483	-206	<0.01	190 ± 158	23	0.29
	Yes	129	239 ± 369			213 ± 205		
Vegetables & Fruit	No	1819	252 ± 253	238	<0.01	195 ± 139	54	<0.01
	Yes	120	490 ± 368			250 ± 184		

Footnote: Mean ± standard deviation of the potassium content of food groups. Serving size as reported in the Branded Product Database. Differences are calculated between the presence and absence of an additive. P-value determined using independent T-test.

3.4.1.3 Sodium content claims and potassium-based sodium substitute occurrence

The Branded Foods Product Database provided an ingredient list for 239,089 products. Of these, 238,043 products did not make a sodium content claim. This resulted in 1046 products with a sodium content claim and included in analysis 1 for the presence of potassium-based sodium substitutes by sodium content claim. Potassium-based sodium substitutes were found in 5719 (2.4%) products without sodium content claims and in 58 (5.5%) products making a sodium content claim ($p<0.01$). The most sodium content claim was unsalted, followed by lightly salted, reduced sodium, low sodium and sodium free (**Figure 3.4**)

Figure 3.4: The proportion of sodium content claims in the Branded Foods Product Database.



There were no very low sodium content claims identified in the Branded Foods Product Database. The proportion of products without sodium content claims which contained a potassium-based sodium substitutes was 2.4%, this was statistically significantly lower than products with a sodium free content claim (at 9.5%, $p=0.003$), products with a low sodium content claim (at 10.3%, $p<0.001$) and products with a reduced sodium content claim (at 23.3%, $p<0.001$) (Table 3). Lightly salted products also had a lower proportion of products with potassium-based sodium substitutes at 0.5% compared to sodium free ($p=0.001$), low sodium ($p<0.001$) and reduced sodium ($p<0.001$) (Table 3.5). Unsalted products also had a lower proportion of products with potassium-based sodium substitutes at 0.6% compared to sodium free, low sodium and reduced sodium products (all $p<0.001$) (**Table 3.5**). All p-values were two-tailed with the Bonferroni correction applied.

Table 3.5: Number of products with sodium content claims and proportion of those without and with potassium-based sodium substitutes from the Branded Foods Product Database

Potassium-based sodium substitutes		No Claim	Lightly salted	Unsalted	Sodium Free	Low sodium	Reduced sodium	Total
Without	Count	232324[a]	214[a]	499[a]	57[b]	96[b]	122[b]	233312
	% within claim	97.6%	99.5%	99.4%	90.5%	89.7%	76.7%	97.6%
With	Count	5719[a]	1[a]	3[a]	6[b]	11[b]	37[b]	5777
	% within claim	2.4%	0.5%	0.6%	9.5%	10.3%	23.3%	2.4%
Total	Count	238043	215	502	63	107	159	239089
	% within claim	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

[a,b] Each subscript letter denotes a subset of sodium content claim whose column proportions do not differ significantly from each other at the .05 level (with Bonferroni correction applied).

The Branded Foods Product Database includes 13,236 products with non-missing values for potassium and sodium concentration. From these, 251 items were excluded as they could not be coded into a sodium category because they contained more than 140mg of sodium and there are no sodium reduction targets for these specific foods. The food items excluded were beverages (n=75), condiments (n=19), eggs and dairy (n=26), grains (n=26), snacks (n=60), supplements (n=36) and vegetables and fruit (n=9). Nine products had missing serving sizes. This resulted in 12,976 products meeting inclusion criteria for analysis 2, exploring sodium and potassium concentration. Of these, 4003 products had a serving size at or less than 30g so mineral concentration was explored using mg per 100g. The remaining 8973 products had serving sizes above 30g, so mineral concentration was exploring using mg per serving size.

Across all sodium categories, potassium-based sodium substitutes were found in 414 (3.1%) of food items. Products with potassium-based sodium substitutes had more ingredients and larger serving sizes than products without potassium-based sodium substitutes (23 (15-42) vs

11 (4-20), p<0.01 and 85 (50-194) vs 56 (30-128), p<0.01, respectively). Additionally, a higher proportion of products with potassium-based sodium substitutes were considered ultra-processed (had more than 5 ingredients) versus products without potassium-based sodium substitutes (395/414 (95.4%) vs 8589/12562 (68.4%), p<0.01). Potassium-based sodium substitutes were found in 49.4% of products above sodium reduction targets. This was statistically significantly higher than the proportion of products below sodium reduction targets at 44.3% (p<0.05). Both of these proportions were higher than the proportion of products with potassium-based sodium substitutes in the 35-140mg sodium categories at 5.3%, 6-35mg of sodium at 0.2% and 5 or less mg of sodium at 0.7% (all p<0.05).

As noted above, for the FDA guidelines products with small serving sizes (30g or less) the sodium concentration is considered by 100g. In the Branded Foods Product Database, 4003 items with small serving sizes had non-missing values for sodium and potassium concentration, of these 40 (1.0%) of products contained potassium-based sodium substitutes. For all products with small serving sizes, products with potassium-based sodium substitutes had a 338mg per 100g higher median sodium concentration and a 283mg per 100g higher median potassium concentration (both p<0.01) (Table 4). Statistical testing was not performed on products with less than 140mg of sodium as the number of food products containing potassium-based sodium substitutes within these categories was too small to support this type of analysis (**Table 3.6**). The three products under 5mg of sodium containing potassium-based sodium substitutes were potassium-based table salts. These products are very high in potassium, as they are approximately 50% potassium by weight. For products above 140mg of sodium, there was a statistically significant higher concentration of potassium and sodium in products above sodium reduction targets with potassium-based sodium substitutes versus those without. The difference

in potassium for products below sodium reduction targets with and without potassium-based sodium substitutes was not statistically significantly different, however the concentration of sodium was statistically significantly higher among products with potassium-based sodium substitutes.

Table 3.6: Sodium and potassium concentration mg per 100g for products with small serving sizes (30 grams or less) of foods with different levels of sodium and without and with potassium-based salt substitutes

Sodium Category	N (%)		Sodium (mg/100g), median (interquartile range)		p-value [a]	Potassium (mg/100g), median (interquartile range)		p-value [a]
	Without PBSS	With PBSS	Without PBSS	With PBSS		Without PBSS	With PBSS	
<5mg	487 (99.4%)	3 (0.6%) [b]	0 (0-0)	0 (0-0)	n/a [c]	446 (100-750)	49286 (49258-49286)	n/a [c]
5-35mg	159 (100%)	0	21 (17-28)	n/a	n/a [c]	100 (1-533)	n/a	n/a [c]
36-140mg	385 (100%)	0	100 (67-139)	n/a	n/a [c]	200 (129-350)	n/a	n/a [c]
Above 140mg								
Below sodium reduction targets	1051 (99.2%)	9 (0.8%)	383 (276-536)	667 (536-796)	<0.01	296 (143-643)	536 (357-571)	0.127
Above sodium reduction targets	1881 (98.5%)	28 (1.5%)	667 (482-875)	767 (732-1000)	<0.01	183 (107-483)	473 (200-607)	<0.01
All categories	3963 (99.0%)	40 (1.0%)	429 (167-679)	767 (679-922)	<0.01	217 (111-607)	500 (235-634)	<0.01

[a] P-value calculated using independent samples Mann-Whitney U-test foods with and without potassium-based sodium substitutes.
[b] Products are potassium-based table salts
[c] P-value not calculated due to low sample size.

Table 3.7: Sodium and potassium concentration mg per serving for products with larger serving sizes (>30 grams) of foods with different levels of sodium and without and with potassium-based salt substitutes

Sodium Category	N (%)		Sodium (mg/serving), median (interquartile range)		p-value [a]	Potassium (mg/serving). median (interquartile range)		p-value [a]
	Without PBSS	With PBSS	Without PBSS	With PBSS		Without PBSS	With PBSS	
<5mg	1286 (100.0%)	0 (0.0%)	0 (0-0)	n/a	n/a [c]	160 (95-300)	n/a	n/a [c]
5-35mg	1415 (99.9%)	1 (0.1%) [b]	14 (10-20)	24 (24-24) [b]	n/a [c]	150 (81-280)	0 (0-0)	n/a [c]
36-140mg	2619 (99.2%)	22 (0.8%)	90 (64-120)	139 (104-139)	<0.01	190 (200-303)	425 (229-629)	<0.01
Above 140mg								
Below sodium reduction targets	1272 (88.0%)	174 (12.0%)	260 (182-345)	410 (210-600)	<0.01	180 (103-280)	355 (230-509)	<0.01
Above sodium reduction targets	2007 (91.9%)	177 (8.1%)	350 (220-520)	510 (410-670)	<0.01	120 (60-200)	270 (150-510)	<0.01
All categories	8599 (95.8%)	374 (4.2%)	103 (15-240)	460 (260-649)	<0.01	160 (84-280)	320 (170-511)	<0.01

[a] P-value calculated using independent samples Mann-Whitney U-test foods with and without potassium-based sodium substitutes.
[b] Product is a club-soda beverage
[c] P-value not calculated due to low sample size.

For products with serving sizes above 30g, the potassium and sodium content is considered by serving size as per FDA guidelines. Of the 8,973 products with larger serving sizes and non-missing values for sodium and potassium concentrations, 374 (4.2%) contained potassium-based sodium substitutes. For all products with larger serving sizes, products with

potassium-based sodium substitutes had a 357mg per serving higher median sodium concentration and a 160mg per serving higher median potassium concentration (both $p<0.01$) (**Table 3.7**). Statistical testing was not performed on products with 35mg or less sodium due to small sample sizes. However, for all other sodium categories, both potassium and sodium concentrations were higher in products containing potassium-based sodium substitutes versus products without potassium-based sodium substitutes.

3.4.2 Phosphorus Additives

Phosphorus additives with the word "phos" were found in 46,356 (19.4%) items. Lecithin additives were found in 44,144 (18.5%) items, though of these 15,899 (6.6%) products contained both "phos" additives and lecithin. Phosphorus content information was available for only 3,466 (1.45%) food items and these products were used in the analysis. Of the items reporting phosphorus content, 1,791 (51.6%) contained additives. Some products contained more than one phosphorus additives. Seven products contained five unique phosphorus additives, six of these products were breakfast shakes and one was soymilk.

3.4.2.1 Types of lecithin and phosphorus additives and foods they were found in

The most common lecithin type was soy lecithin, occurring as the first lecithin additive in 1,268 of items providing phosphorus content, 56 items reported sunflower lecithin, and in three instances, the first lecithin additive type was unspecified. The most common phosphate salt was calcium phosphates, followed by sodium phosphates, ferric (iron) phosphates, and potassium phosphates (**Table 3.7**). Of particular interest for adults with kidney disease are potassium and sodium based salts as these are also nutrients of concern for this population.

Table 3.7: Types of phosphorus additives found in the subset of the Branded Foods Product Database providing phosphorus content

Phosphorus Salt	First Phos Additive	Second Phos Additive	Third Phos Additive	Fourth Phos Additive	Total (%)
Calcium phosphates	417	398	16	0	828 (45%)
Sodium phosphates	612	47	2	0	661 (36%)
Ferric phosphates	77	51	17	17	162 (9%)
Potassium phosphates	85	35	4	1	125 (7%)
Magnesium phosphates	11	29	0	1	41 (2%)
Other	7	1	0	0	8 (<1%)

Phos – phosphorus; Other includes: phosphorus acid (2), aluminum phosphate (1), pyrophosphate (4), phosphate – unspecified (1).

There were differences observed between food types and the proportion of foods with additives. Minimally processed foods do not contain additives. A higher proportion of ultra-processed beverages, dairy products and non-dairy alternatives contained phosphate salts than compared to other food categories (**Table 3.8, Figure 3.5 – panel A**). A higher proportion of ultra-processed grains and nutrition/protein supplements contained lecithin compared to other food categories. A higher proportion of ultra-processed beverages, grain products and nutrition/protein supplements contained both lecithin and phosphate salts compared to other food categories.

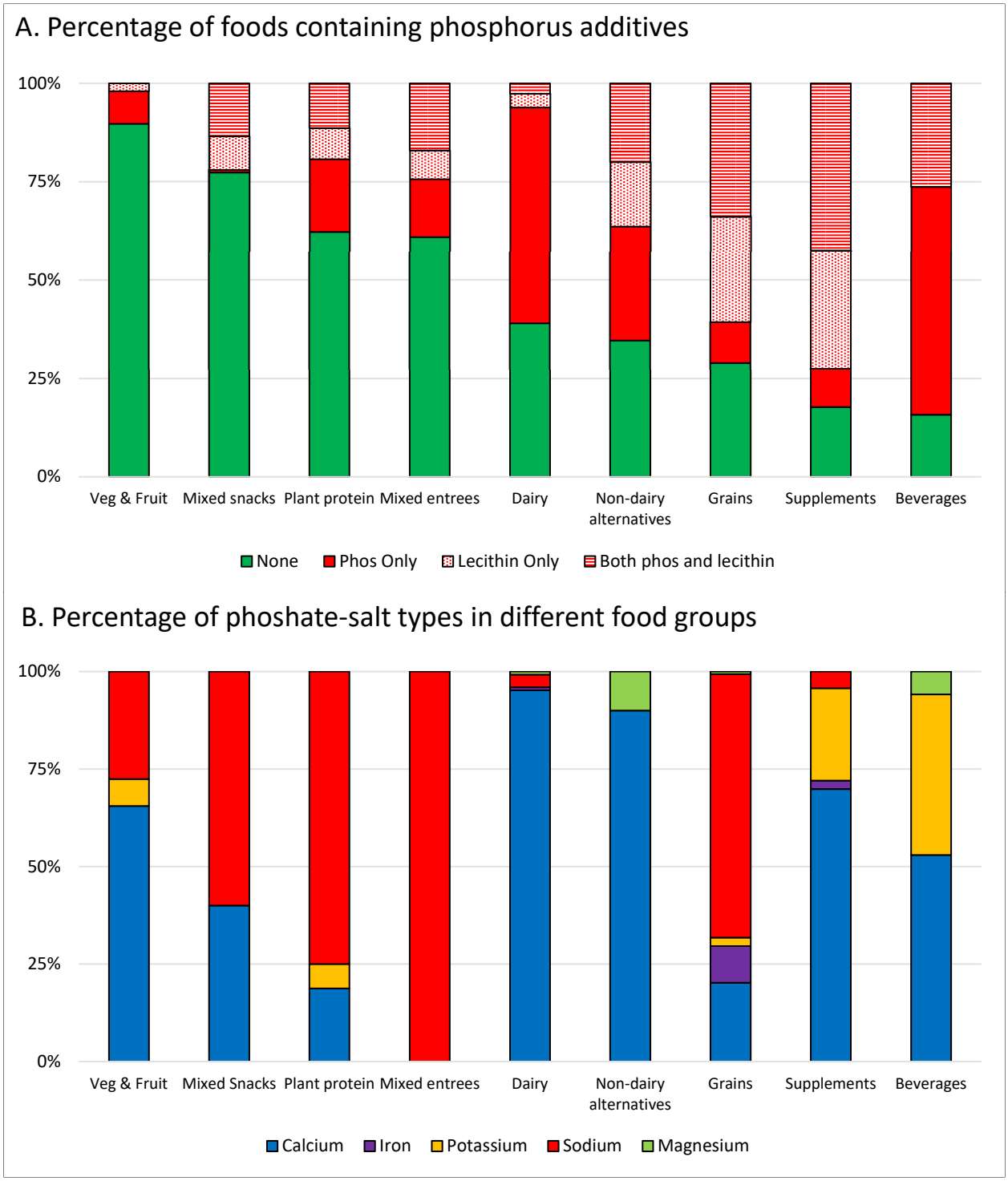
When phosphorus salts were used, different foods categories used different salts. Non-dairy and dairy products predominantly use calcium phosphates. Mixed foods (entrees and snacks) and processed plant proteins use sodium phosphates more often (**Figure 3.5 – panel B**). Potassium phosphates were used most frequently in processed beverages, protein supplements and nutrition supplements. Iron phosphates were more commonly found in grain products. Magnesium phosphates were only found in dairy products, supplements, and processed plant proteins.

Table 3.8: Types of additives found in different food categories

Product type	Total Products	Without Additives, n (%)	With additives, n (%)	Additive type		
				Phosphorus Only, n (%)	Lecithin Only, n (%)	Phosphorus & Lecithin, n (%)
Minimally processed foods						
Fruits and vegetables	112 (100%)	112 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Animal proteins	44 (100%)	44 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Plant proteins	186 (100%)	186 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grains	72 (100%)	72 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dairy Products	66 (100%)	66 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ultra processed foods						
Beverages	19 (100%)	3 (15.8%)	16 (84.2%)	11 (57.9%) *	0 (0.0%)	5 (26.3%) *
Dairy	226 (100%)	88 (38.9%)	138 (61.1%)	124 (54.8%) *	8 (3.5%)	6 (2.7%)
Non-dairy alternatives	55 (100%)	19 (34.5%)	36 (65.5%)	16 (29.1%) *	9 (16.4%)	11 (20.0%)
Meat Alternatives	114 (100%)	71 (62.3%)	43 (37.8%)	21 (18.4%)	9 (7.9%)	13 (11.4%)
Fruit &vegetables	347 (100%)	311 (89.6%)	36 (10.3%)	29 (8.4%)	7 (2.0%)	0 (0.0%)
Grain	1767 (100%)	509 (28.9%)	1258 (71.2%)	186 (10.5%)	473 (26.8%) *	599 (33.9%) *
Mixed Entrees	82 (100%)	50 (61.0%)	32 (39.0%)	12 (14.6%)	6 (7.3%)	14 (17.1%)
Mixed Snacks	141 (100%)	109 (77.3%)	32 (22.7%)	1 (0.8%)	12 (8.5%)	19 (13.5%)
Nutrition & protein supplements	186 (100%)	33 (17.8%)	153 (82.3%)	18 (9.7%)	56 (30.1%) *	79 (13.5%) *

* Denotes statistically significantly higher proportion of products with a phosphorus additive compared to products without additives.

Figure 3.5: Panel A - Percentage of foods categories which contain either no additives, phosphorus salts only, lecithin only or both phosphorus salts and lecithin. **Panel B –** percentage of phosphate salt makeup among products that contained phosphate salts across food categories.

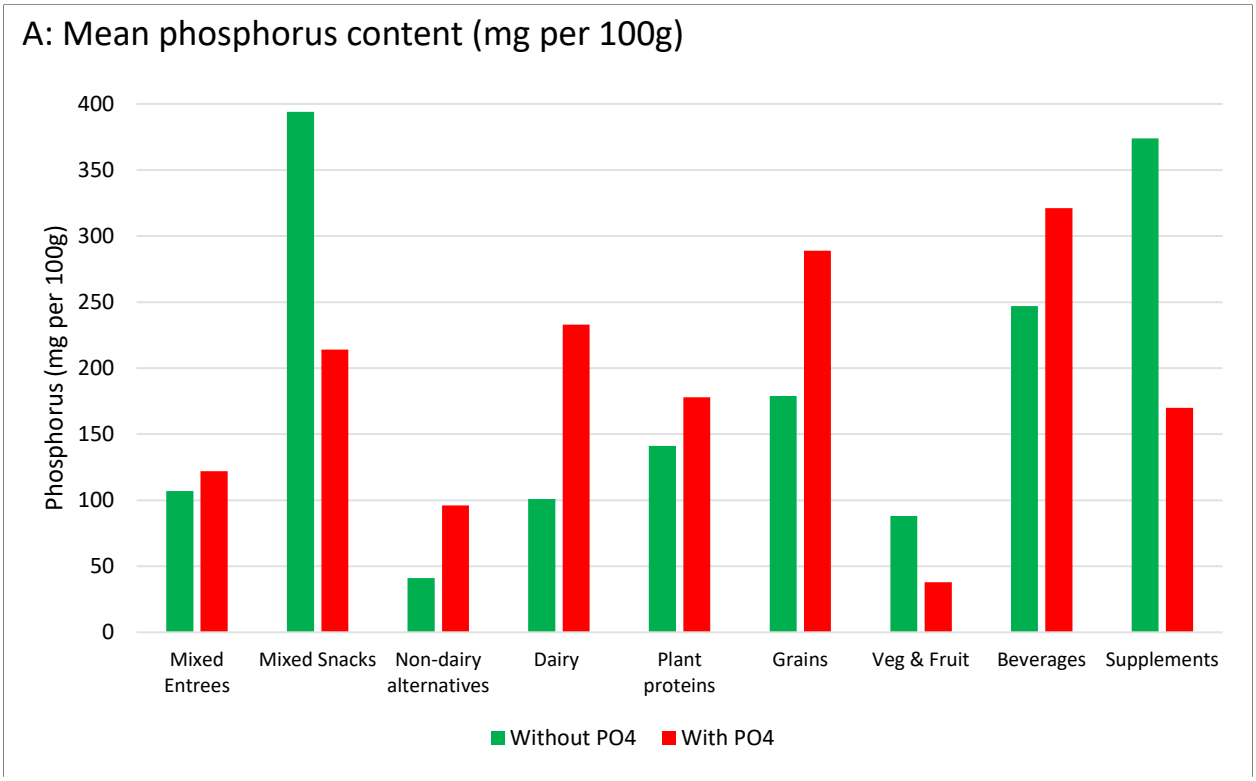


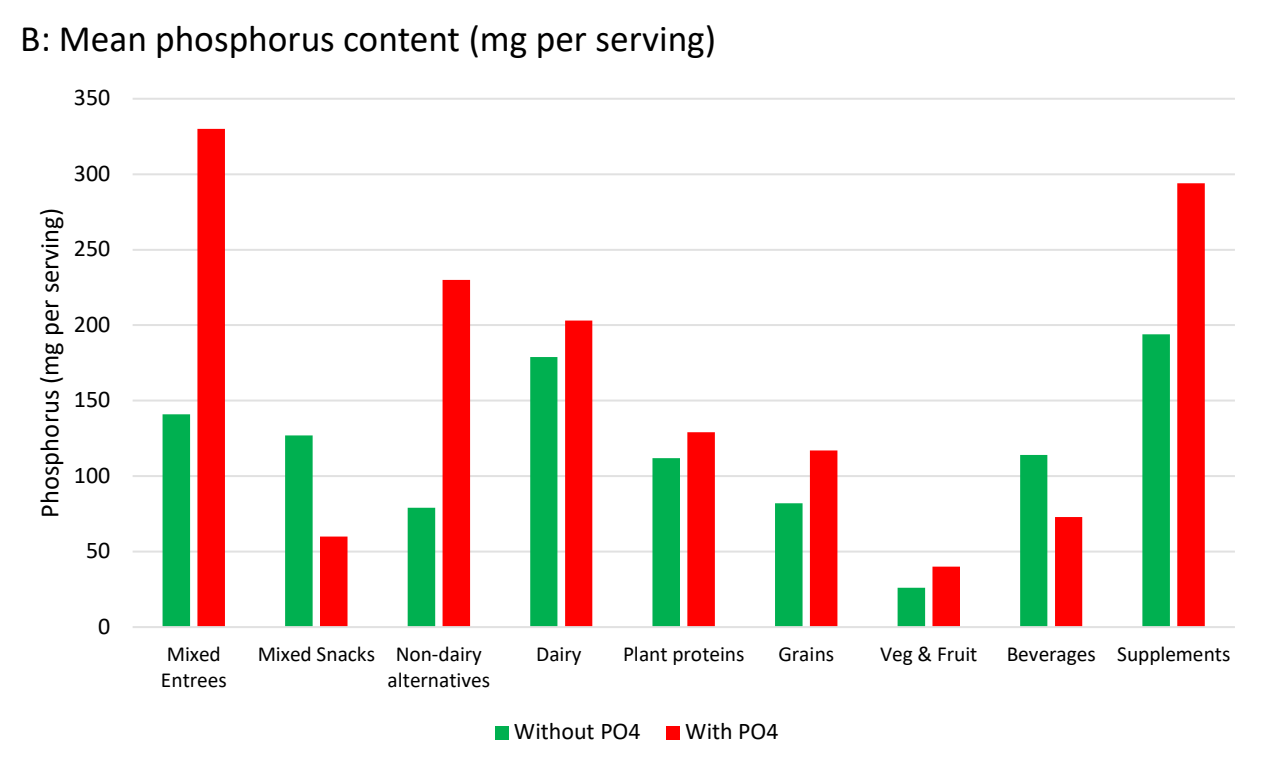
3.4.2.2 The impact of additives on phosphorus content

Across all products, products with lecithin only had a lower phosphorus content than products without additives (86 (54-200) vs 145 (77-351) mg per 100g, $p<0.01$). Surprisingly, median phosphorus content was lowest in products with only added lecithin than in products without any phosphorus additives (86 (54-200) vs 145 (77-351) mg per 100g, $p<0.01$), which was not different from products with phosphate salts (176 (101-276) mg per 100g, $p=0.22$) or products with both phosphate salts and lecithin (161 (99-285) mg per 100g, $p=1.00$).

The impact of a phosphorus salt on phosphorus content (mg per 100) was explored among ultra-processed products grouped by similar phosphorus contents. The phosphorus content of non-dairy alternatives, dairy, plant proteins, and grains were significantly higher when the product contained a phosphate salt compared to products without a phosphate salt (**Figure 3.6**). When phosphorus content was considered by serving, mixed entrees, non-dairy alternatives, grains, vegetables and fruits with phosphate salts all had statistically significant greater phosphorous content compared with similar products without phosphate salts. For supplements, which includes protein powders, meal replacement or protein drinks, when phosphorus content was considered by 100g, products without additives contained more phosphorus, though this relationship reversed when phosphorus content was considered by serving – both differences were statistically significant.

Figure 3.6: The mean phosphorus content per 100g (panel A) and per reported product serving size (panel B) across ultra-processed food categories for products with and without phosphate salt (PO4) additives. * indicates $p<0.05$ as determined by Mann-Whitney U-test.

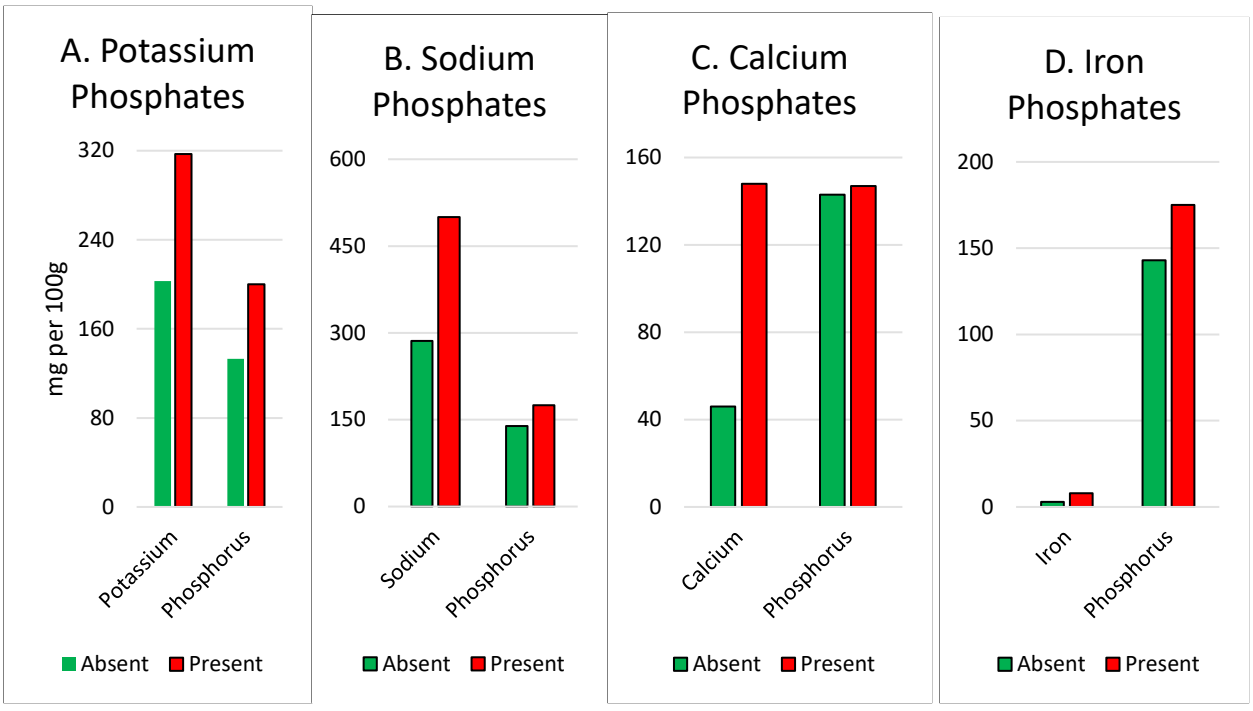




3.4.2.3 The correlation between phosphorus and other mineral content

The most common phosphate salts identified in the Branded Foods Product Database were calcium, iron, potassium and sodium based. When a product contained a phosphate salt both the phosphorus and co-mineral (potassium, calcium, sodium and iron) content (mg per 100g) were statistically significantly higher (**Figure 3.7**) than products without this phosphate salt. The Spearman's rho correlation coefficient between phosphorus and potassium content (mg per 100g) when a product contained potassium phosphate was higher compared to products without potassium phosphates (0.81 vs 0.53). The same was true of sodium and phosphate in products with and without sodium phosphates (0.45 vs 0.07), calcium and phosphate in products with and without calcium phosphates (0.47 vs 0.32) and iron and phosphates in products with iron phosphates (0.47 vs 0.33). All correlations were considered statistically significant ($p<0.05$).

Figure 3.7: Median phosphorus content (mg per 100g) and potassium (panel A), calcium (panel B), sodium (panel C) and iron (panel D) content (mg per 100g) among all food products with and without potassium phosphates (panel A), calcium phosphate (panel B), sodium phosphate (panel C) and iron phosphates (panel D) additives. * indicates $p<0.05$ as determined by Mann-Whitney U-test.



3.5 Discussion

The prevalence of potassium and phosphorus additives and how their presence changes mineral content is not well documented. The USDA's Branded Foods Product Database contains ingredient lists and nutrition information for 239,089 unique food items. Of these, 14.7% contained potassium additives and 31.2% contained phosphorus additives, however less than 6% of these foods report potassium content and less than 2% report phosphorus content. This makes understanding how potassium and phosphorus content is impacted by additives challenging.

There is growing concern that potassium and/or phosphorus additives in processed foods can significantly increase dietary potassium and/or phosphorus intake and it has been suggested that teaching strategies targeting additive avoidance is warranted.[11] Current handouts for low potassium diets tend to focus on restriction of minimally processed foods, most often targeting fruits and vegetables.[29] Current handouts for low phosphorus focus restriction on plant proteins and minimally processed dairy products.[79] However, healthy diet patterns, such as the Mediterranean Diet, are associated with improved health outcomes in the general population and adults living with CKD.[61,87] Therefore diet strategies for potassium and phosphorus management that target less healthy foods may help reduce healthy food restrictions, which may make the adoption of healthy diet patterns easier for this population.

3.5.1 Potassium Additives

Specific to potassium additives, there were 34 unique potassium additives found in the entire Branded Foods Product Database. Some potassium additives, such as potassium sorbate, are highly prevalent, while others are less so. In the subset Branded Foods Product Database that reported potassium content there were 16 potassium additives, however only 9 additives were prevalent enough to enable analysis for potassium content. This means the majority of potassium

additives were not represented in the subset Branded Foods Product Database and therefore there is no information on how they may change potassium content. Additionally, we found that the use of multiple potassium-based additives was not uncommon. These findings highlight just how challenging it is for clinicians and patients to understand how potassium additives may impact potassium content of foods.

With regards to where potassium additives were added, we found that additives were in every food group and most food categories. Though due to the diversity of products in the Branded Foods Product Database and the large quantity of food categories required to describe this diversity (such that items with similar natural occurring potassium content were grouped together) in the end there were relatively small numbers in each food category. This prohibited the use of statistical analysis and therefore firm conclusions cannot be drawn about how potassium additives in specific food categories may impact potassium content. However, in our study we found that many meat, fish and poultry products with additives had a higher potassium content, which has also been reported in other studies.[88,89] Additionally, we found higher potassium contents in both broths and canned soup, which has also been previously reported.[90]

One of the study objectives had been to investigate how different additives impact potassium content to see if some potassium additives may be more likely to increase potassium. However, due to the diversity of both potassium additives and food categories in the Branded Product Database understanding this remains elusive. In our study, we found acesulfame potassium, potassium benzoate and potassium iodate/iodine were associated with lower potassium content than foods without additives. Potassium carbonates and potassium sorbate were not associated with increased potassium content. Potassium chloride, potassium citrate, potassium phosphates and potassium lactate all appeared to be associated with higher potassium

content. That some additives appear to be associated with lower potassium content is likely an artifact of two things. First, when we did our analysis, we compared the mean of all products without additives, to means of all the products that contained that specific additive. This type of analysis does not allow for any consideration of natural occurring potassium in the food items. Our original intent had been to complete a sub-group analysis by grouping foods into unique enough groups to control for naturally occurring potassium content, however when this level of grouping was completed, group sizes were too small to allow for statistical testing to be performed. Different additive types are used in different foods. For example, acesulfame potassium is often used in highly-processed sweet foods which would contain very little natural occurring potassium. This, in comparison to potassium lactate which is often used in meat, fish and poultry products, products that contain significant amounts of natural occurring potassium. Second, how much of an additive is being added to a food item will depends on the role of the additive in the food item.[29] Regulations stipulate specific amounts of potassium additives that can be added to food based on their function.[29] Potassium additives are approved for many different uses in many different foods.[29] Further studies are needed to investigate how each additive impacts potassium content in each specific food they are used in. To do this, chemical analysis of a large sample of similar foods with the same additive type is needed.

Another interesting finding from our study was the average potassium content of foods, regardless of the presence of additives. As previously noted, low potassium patient education materials tend to predominantly restrict unprocessed and minimally processed fruits and vegetables and less often restrict potassium in processed or animal-based foods.[29] However, our results did not demonstrate that the potassium content of minimally processed fruits and vegetables was the highest. Instead, we found that the highest potassium content occurred in

prepared mixed foods when potassium content was considered per serving or in beverages and condiments when potassium content was considered as mg per 100g. Additionally, food groups that were more likely to have a higher potassium content when additives were used included grain products, mixed foods and processed fruits and vegetables.

With regards to our sample menu, we demonstrated that a menu consisting of foods that contain additives compared to foods that did not contain additives resulted in a 1874mg (66%) increase in total potassium content. While this increase would certainly be considered clinically significant, it is worth noting that these simulations have limitations. For example, in the case of similar simulation studies with phosphorus additives [91,92] higher phosphorus intakes at 1500-1800mg was reported compared to studies that investigate dietary intake using food recalls or biomarkers at 1000-1400mg.[93-95] Therefore, it is probable that the estimates derived from this simulation analysis could similarly be overestimating potassium. Regardless, even if there is a net overestimation, the menu does demonstrate that if a patient did not look for potassium additives, they may inadvertently significantly increase their potassium intake by unknowingly choosing foods with these additives. This suggests that teaching strategies for hyperkalemia could include teaching patients how to identify potentially problematic additives in foods.

Potassium has been identified as an ideal candidate for sodium replacement in processed foods. Therefore, we hypothesized that processed foods which had undergone sodium reformulation may be more likely to contain potassium additives, potassium chloride and potassium lactate specifically. We demonstrated when a sodium content claim was absent, or there was a lightly or unsalted content, there was a lower occurrence of potassium-based sodium substitutes in these groups compared to the reduced sodium, low sodium and sodium free content claim groups. These differences were statistically significant. Provided the natural-occurring

potassium and sodium concentration of these foods was low, these would be suitable options for adults requiring concurrent potassium and sodium restrictions. The use of potassium-based sodium substitutes is associated with a 160mg per 100g higher potassium concentration, which may be clinically relevant for adults who needs to limit their potassium intake (e.g. adults with kidney disease or heart failure), as individuals consuming these foods may be more likely to exceed their potassium intake targets.

An interesting finding for this analysis was that products with potassium-based sodium substitutes contained more sodium than products without. One possible explanation for this is the types of foods that contain potassium-based sodium substitutes. Products with potassium-based sodium substitutes had a higher proportion of ultra-processed foods, which have been previously reported to be higher in sodium than minimally processed foods.[2] **This suggests that for those requiring concurrent potassium and sodium restriction recommendations to consume low potassium, minimally processed foods may be better than looking for ultra-processed foods that have undergone sodium reformulation.**

However, given that for many Canadians more than 50% of energy intake comes from ultra-processed foods[1], teaching patients how to identify which ultra-processed foods are more likely to be acceptable for low potassium and sodium diets is an important component of medical nutrition therapy. Within the Branded Foods Product Database, products with a reduced sodium, low sodium and sodium free content claims contained the highest proportion of products with potassium-based sodium substitutes. This suggests that for this population recommendations to pay particular attention to foods with these sodium content claims appears prudent.

3.5.2 Phosphorus Additives

Specific to our analysis of phosphorus additives, it was an unexpected finding that lecithin was not consistently associated with higher phosphorus content. This may be explained by the amount of phosphorus in lecithin. Pure lecithin has been reported to be 20% phosphorus by weight [82], however when lecithin is used as an additive, it was reported that phosphorus only made up 8% of the lecithin.[82] Alternatively if the amount of lecithin added to these foods is very small, there will be little impact on phosphorus content. However, it is also possible that the phosphorus content in the Branded Foods Product Database is under-reported. Several other studies comparing phosphorus content listed in nutrient databases of animal products with phosphorus additives to amounts analyzed in labs indicate that nutrient databases did not accurately reflect phosphorus contents of these foods.[26,96,97] Whether the same is true for other food products (eg ultra-processed grain products or mixed meals) is unknown and appears to be an important area for further study.

A novel aspect of this analysis was the exploration of how the use of different phosphorus salts impacts the associated mineral content (for example how potassium content is impacted by potassium phosphate additives). While there were differences in the extent of the correlation between the nutrients we investigated, it was an interesting finding that for all minerals, when the specific salt was used, there were concurrent increases in both the target mineral and phosphorus content. This was not entirely unexpected as salts such as potassium phosphates, calcium phosphates and ferric phosphates are added to products for fortification. This can be seen by where these additives may be found, such as potassium phosphates in nutrition supplements, calcium phosphates in non-dairy alternatives and iron phosphates in grains.

Elucidating the relationship between phosphorus and other minerals may have particular benefit for patients and clinicians. Sodium, potassium, iron, and calcium are all nutrients that

appear on the new nutrition facts tables. For products that contain any of these types of salts, our data provides a signal, that as the accompanying mineral increases, so too will the phosphorus content. Furthermore, potassium and sodium may also be nutrients of concern among individuals with reduced kidney function and identifying foods containing high amounts of these minerals may be important. **Therefore, a potential phosphorus reduction strategy may be to review ingredients lists for calcium, sodium, iron, and/or potassium phosphate and consider how much of the other mineral is present. High amounts of the corresponding nutrient on the nutrition facts table potentially suggests products that are also higher in phosphorus.**

3.5.3 Limitations of this type of research using the BFPD

Our analyses of the BPFD has limitations. Specific to our potassium analysis, one limitation is that we have not considered the bioavailability of the potassium additives. For example, case reports have reported that dietary potassium chloride and medicinal potassium citrate supplements have been associated with hyperkalemic events.[98,99] Whereas acesulfame potassium tends to be undigested, passing through the body as a complete metabolite [100] suggesting that the likelihood of acesulfame potassium being associated with hyperkalemia is quite low. Ultimately, as the use and diversity of potassium additives grow, this will likely become an increasingly important area for further research.

Specific to our analysis of sodium content claims, one limitation identified was how products were identified. In this case, only text in the product description of the Branded Foods Product Database was reviewed as opposed to front packages/labels of products. In a 2017 study of household scanning data, it was reported that 2% of items had a “low sodium” content claim.[101] In this analysis, sodium content claims were found for 0.44% of food items, therefore it is possible that some items in Branded Foods Product Database that have sodium claims on their

labels/packages were not flagged as having a sodium content claim. However, as the datasets in this analysis differ, it is possible that the observed difference is related to market share (i.e. that low sodium products are being purchased more often) as opposed to being under-reported in the Branded Foods Product Database.[101] This remains an area for further study. Another limitation was that potassium chloride and potassium lactate were considered as sodium substitutes in every instance it was found in foods, though these additives can be used for different purposes. The Branded Foods Product Database data does not allow for differentiation between potassium-additive use in food products. It is possible that these additives were being used for purposes other than sodium substitution.

Specific to our phosphorus analysis, while our approach has been robust and systematic it is important to recognize that phosphate content is not reported for the vast majority (over 98% of 238,000 individual products) of food products which is a major limitation of using the Branded Foods Product Database. We also did not complete any nutrient analysis to confirm the accuracy of phosphorus reporting in the Branded Foods Product Database. It is important to note that for all phosphorus reporting in the Branded Product Database, phosphorus reporting is given as an approximation, with no entry being reported as an exact amount. Furthermore, within the United States labeling laws, nutrients such as phosphorus are allowed to be underreported but not over-reported.[102] This may mean that phosphorus content is more likely to be under-reported as opposed to over-reported in nutrient databases. Under-reporting of phosphorus content in nutrient databases has been previously reported for animal protein products containing phosphorus additives.[26,96,97] Differences between analyzed and reported values vary. One paper exploring phosphorus to protein ratios reported 225% more phosphorus (from 11.4mg/g to

25.7mg/g) in products without and with phosphorus additives.[97] Therefore, further audits of phosphorus reporting across a variety of food categories appears warranted.

Limitations applicable to all of our analyses using the BFPD is that it is not possible to consider how frequently these foods are consumed by either the general or CKD population. What is known, is that ultra-processed foods make up approximately 55% of energy intake in American adults.[72] A study in Brazil comparing hemodialysis patients to the general population reported a higher intake of processed foods among those on dialysis compared to those who are not.[103] Additionally, a Canadian study of adults living with CKD reported that approximately 60% of energy intake came from processed and ultra-processed foods.[61] One definition of ultra-processed foods is a product that contains 5 or more ingredients.[104] In the subset Branded Foods Product Database, 9,588 (72.4%) of products contained 5 or more ingredients, suggesting that the information in the Branded Foods Product Database predominantly reflects ultra-processed foods, which makes up the majority of energy intake in America.

Another limitation of these studies is that we used the serving sizes as provided by the Branded Foods Product Database to compare mineral content per serving. This is not a standardized amount and there was notable variability, even within comparable products which suggests that relying on this number alone should be done with caution. To help correct for this, we also considered potassium content per 100g. However, the potential concern with this method is that 100g may be an improbably high amount of food to eat in some categories, such as condiments or drink mixes. Conversely, it may be an unreasonably low amount of food to eat, in the case of dairy or meat products. Ultimately, to understand how a food contributes to total daily intake consideration should be given to how much of the product a person is consuming.

While the food industry is encouraged to provide information for the database, it is voluntary and therefore may not reflect all sectors of the food supply equally, for example from smaller or independent businesses. Another limitation is that our search was conducted using only the 2018 Branded Foods Product downloadable database. The USDA continues to update and upgrade their nutrition information and now has the Global Branded Foods Product Database[105], which could enable greater global applicability.[106] Additionally, countries such as Finland, which have Foodie.Fi[107], and Canada, which has the Food Label Information Program database[108] are other potential data sources for this type of research.

3.6 Conclusion

Our study demonstrates that potassium and phosphorus additives are prevalent, diverse and widespread. However, with less than 6% of food items reporting potassium content, and less than 2% reporting phosphorus content, understanding how much is in foods is a major challenge. However, these preliminary results suggest that when potassium additives are present, that the potassium content of vegetables and fruits, grain products, condiments, beverages and mixed foods may have higher potassium contents that when additives are not present. The use of potassium-based sodium substitutes is associated with a median increased potassium content of 100mg per 100g. When products were grouped by natural phosphorus content, in ultra-processed dairy and non-dairy alternatives, plant proteins and grains, the presence of phosphate salts was associated with increased phosphorus content. Given the prevalence of additives and the potential impact they have on potassium and phosphorus content, teaching patients to read ingredients lists for these additives appears warranted.

Chapter 4: Diet quality scores and health outcomes in CKD

4.1 Abstract

Background and Aims: How diet quality impact health outcomes in patients with both diabetes and kidney disease is not well known. Furthermore, how well diet quality tools assess nutritional adequacy and correlate with potassium and phosphorus (nutrients of interest in CKD) remains unknown. For analysis one, our aim was to investigate the association between diet quality, using Mediterranean Diet Scores (MDS) and health outcomes. For analysis two, our aim was to investigate how three unique diet quality tools assess nutritional adequacy and correlate with potassium and phosphorus. The three diet quality assessment tools used were Mediterranean Diet Scores (MDS), Healthy Eating Index (HEI) and Healthy Food Diversity (HFD).

Methods: This is a post-hoc analysis of an RCT and longitudinal study investigating adults living with diabetes and chronic kidney disease (CKD).[63,64] Diet quality scores were calculated annually. MDS was analyzed for correlation with lipids, HbA_{1c}, serum potassium, health-related quality of life (HRQOL), depression and nutrient intake. MDS, HEI and HFD were analyzed for correlation with nutrient intake.

Results: 178 diet records from 50 patients who attended two or more visits were included. Mean MDS was moderate (4.1 ± 1.6) and stable over time. Stage 1-2 vs 3-5 CKD had lower raw MDS (3.8±1.5 vs 4.6±1.5, $p<0.001$). Hyperkalemia was associated with raw MDS scores (3.6±1.6 vs 4.2±1.5, $p=0.03$) but not energy adjusted MDS. MDS was not associated with HbA_{1c} or lipids. High vs low MDS was associated with improved HRQOL (mental health 84.4 ± 14.3 vs 80.3 ± 17.1, $p<0.05$; general health 62.6 ± 21.0 vs 56.3 ± 19.8, $p<0.001$) and fewer depressive symptoms (9.1 ± 7.4 vs 11.7 ± 10.6, $p=0.01$). Compared to HEI and HFD, MDS was poorly correlated with nutrient intake (all r-values <0.40). HFD and HEI were moderately correlated

with potassium (r=0.66, p<0.01 and r=0.57, p<0.01). HEI was weakly correlated with phosphorus (r=0.365, p<0.01).

Conclusions: Low Mediterranean Diet scores were associated with reduced kidney function and health related quality of life, but not to other markers of cardiovascular risk. MDS, as a diet quality tool, recommends moderation of dairy and meat which may have specific benefits for CKD as these are both sources of phosphorus. As such high MDS, compared to high HEI and HFD, were associated with lower phosphorus intake. Further studies are needed to understand the nature and direction of the association between diet quality, disease outcomes and nutritional adequacy in this population.

4.2 Introduction

Diabetes and chronic kidney disease (CKD) increase the risk for cardiovascular disease (CVD) and adverse health outcomes. In the general population, Mediterranean diets are associated with improved outcomes[109,110]. Recently, the Kidney Disease Improving Global Outcomes (KDIGO) [11], Kidney Disease Outcome Quality Initiation (KDOQI) [20] and the European Dialysis and Transplant Association (ERA-EDTA) [87] highlighted the importance of diet quality for the CKD population, with the ERA-EDTA specifically suggesting that the Mediterranean Diet be considered the diet of choice for adults living with CKD [87].

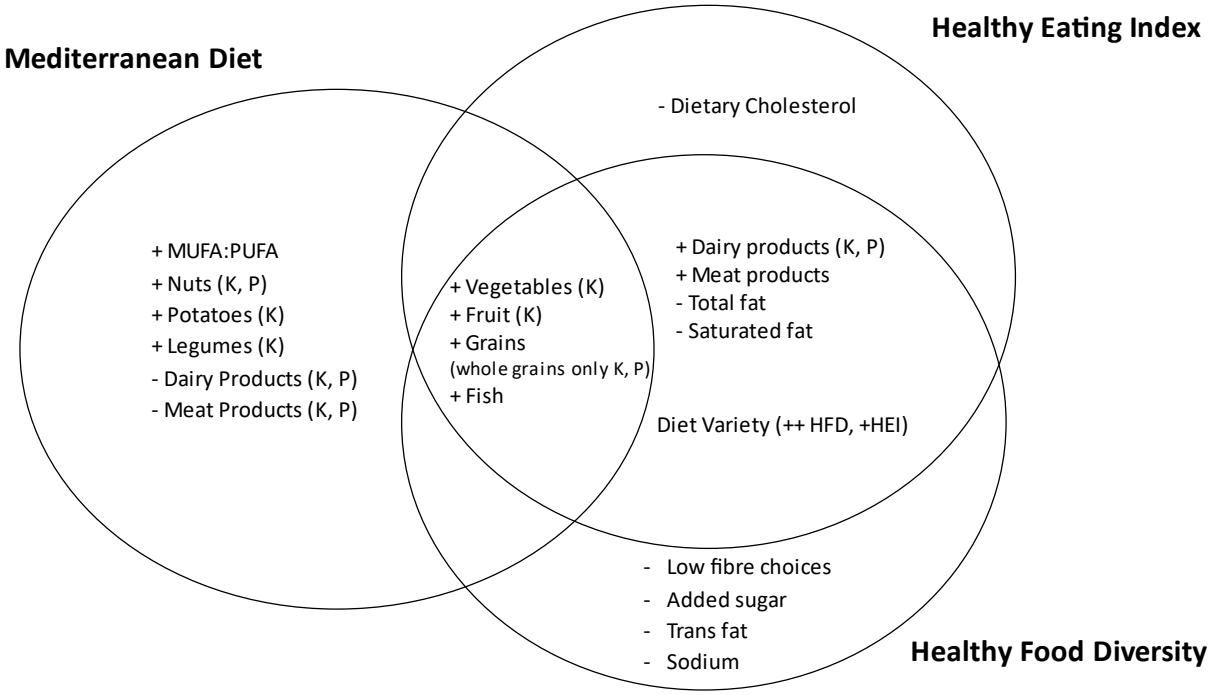
Mediterranean-style diets are higher in potassium than traditional western diets [111]. This may make it more challenging for the CKD population to follow a Mediterranean diet as they may have been advised to lower their potassium intake to prevent or manage hyperkalemia. [11] Yet, evidence does not suggest that Mediterranean-style diets, high in plant foods, are necessarily associated with increased serum potassium levels or hyperkalemia. [87,112] This may in part be

related to the low bioavailability of potassium from whole, unprocessed foods coupled with the high bioavailability of potassium additives in processed food. [29,30,113]

Another consideration of optimal diet recommendations is nutritional adequacy. Renal dietitians are responsible for monitoring nutritional adequacy and quality of the diet, in addition to recommending therapeutic diet modifications.[20,114] For dietitians working with adults living with diabetes and chronic kidney disease (CKD), therapeutic modifications can be numerous and may include sodium, phosphorus, protein and carbohydrate modifications, in addition to potassium restriction.[10,21,115]. In earlier stages of CKD, modifications may focus more on carbohydrates and sodium, however as CKD progresses, modification of potassium and phosphorus may be indicated. Dietitians may be more likely to recommend/prescribe renal diets than examine nutrient deficiency [114] and reports have found that counselling by renal dietitians is not consistently associated with improvements in diet quality.[116]

The 2020 KDOQI nutrition practice guidelines recommend that dietitians assess micronutrient intake.[20] The specific suggestions for micronutrient assessments include using a 24-hour recall, nutrition focused physical exam and biochemical analysis [2]. Various diet quality tools, such as MDS [111], Healthy Eating Index (HEI) [117] and Healthy Food Diversity (HFD) [118], have been developed to measure diet quality in the general population. Different diet quality tools classify foods as "beneficial", i.e. food components that increases the score, and detrimental, i.e. food components that decreases the score, differently (**Figure 4.1**). For dietitians, knowing which diet quality tool best describes nutritional adequacy while accommodating potential renal diet prescriptions in advanced CKD (e.g. low potassium and/or low phosphorus diet) would be beneficial.

Figure 4.1 Components of three unique diet quality assessment tools. (+) is a "beneficial category"/food component that increases the score. (-) is a "detrimental category"/food component that decreases the score. For HFD diet variety is denoted with a ++ as this value has a larger impact on the score compared to HEI. Foods traditionally considered high in potassium marked with (K). Foods traditionally considered high in phosphorus marked with (P).



We completed two analyses using data from this cohort. Analysis one had two aims. First, to investigate the relationships between adherence to Mediterranean-style diets, intake of processed foods and intake of foods high in potassium. Second, to investigate the relationships between Mediterranean-style diets, CKD stage and the expression of adverse health outcomes. We hypothesized that adherence to Mediterranean-style diets would be low/moderate and would get worse over time. Additionally, we hypothesized that low MDS would be associated with worse clinical outcomes (hyperkalemia, CVD risk factors, kidney dysfunction and health related quality of life). The aim of analysis two was to compare MDS, HEI and HFD to determine their correlation with nutrient intake in adults living with diabetes and CKD, with a specific focus on potassium and phosphorus.

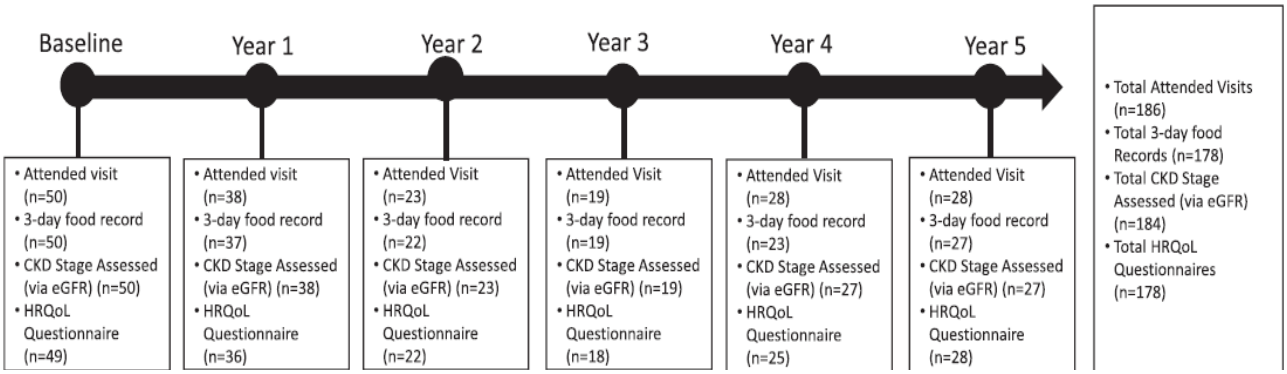
4.3 Methods

4.3.1 Demographics and Anthropometrics

This is a post-hoc analysis from a longitudinal study examining bone health, Health Related Quality of Life (HRQoL) and vitamin D status in adults with diabetes and CKD.[63,64] The original study was an RCT evaluating two different approaches to vitamin D supplementation on the outcomes listed above.[63,64] The RCT included adults (age 18-80 years old), with type 1 or 2 diabetes mellitus and Stage 1-4 CKD with 25 hydroxyvitamin D above 37.5 nmol/L and had no contraindications to vitamin D supplementation.[63,64]

All participants from the RCT (n=120) were offered annual follow up.[63] Of the 120, 50 agreed. Each year participants were invited to attend the Clinical Research Unit at the University of Alberta. There were no significant differences in age, CKD stage, diabetes type or duration between those who agreed to annual follow up and those that did not ($p>0.05$). This longitudinal analysis includes patients with one or more follow up visits between baseline and year 5. Height and weight were measured annually according to standard methodologies.[64] Food records, health status, diagnoses, and medications were reviewed as previously described (**Figure 4.2**).[63,64] The study was approved by the Research Committee of the University of Alberta (PRO00049292).

Figure 4.2 Information collected and the number of participants at baseline and follow up visits.
CKD – chronic kidney disease, HRQoL – health related quality of life, eGFR – estimated glomerular filtration rate.



4.3.2 Dietary Intake

Three-day food records were used to assess intake. If a 3-day food record was not available, 1- or 2-day records were used. There were no significant differences in macro- or micronutrient intake between 3-day food records vs 1- or 2-day records ($p>0.05$). Trained research assistants reviewed food records with participants. Food Processor (Food Processor SQL, v.10.8, ESHA Research, Salem, Oregon, USA) was used to determine nutrient intake. To account for over or under reporting, energy intake was assessed against predicted basal metabolic rate.[119] We considered accurate reporters as those with reported energy intakes within the 95% confidence interval for energy intake/basal metabolic rate.[120]

4.3.3 Dietary Intake Assessment

4.3.3.1 Mediterranean diet scoring – traditional method (used for analysis 1)

To calculate adherence to Mediterranean-style diets, a Mediterranean Diet Score (MDS) was calculated. We used the Trichopoulou 9-point scale [121] , which has been validated and used extensively.[111,121-123] In this scale, the beneficial categories are: high monounsaturated- to saturated- fatty acid ratio (MUFA:SFA), cereals, potatoes, fish, legumes, vegetables, and fruits/nuts[121]; the detrimental categories are dairy and meat.[121] The score is calculated by awarding 1 point for each beneficial category when intake is above the median and 1 point for each detrimental category below the median.[121] The category scores are summed yielding a score between 0 and 9. Foods and beverages not falling in any categories are not calculated in the score.[121] MDS between 0-2 was considered low, 3-5 was considered moderate and 6-9 was considered high.[111]

4.3.3.2 Mediterranean Diet Scoring using standardized scoring cut-offs (used for analysis 2)

Mediterranean Diet Score (MDS) was calculated using a 9-point scale with energy adjusted scoring cut-offs as suggested by Davis et al.[111] This scoring system uses the same beneficial and detrimental categories as the Trichopoulou scale, however instead of using median intakes from the cohort as the cut-offs, standardized cut-offs are used for scoring. Scores were summed to a maximum score of 9. Scores of 0-2 were considered low, 3-5 as moderate and 6 and above as high.[122]

4.3.3.3 Healthy Eating Index Scoring (HEI)

HEI was calculated using a tool adapted for Canada.[117] With HEI adequate intake of beneficial foods (grains, vegetables/fruits, milk and meat) contribute up to 60 points. Moderation scores contribute up to 30 points, for low intakes of total fat, saturated fat and cholesterol. Variety scores contribute up to 10 points if one serving of food from each food group is consumed. The cumulative HEI score is between 0 and 100 with scores less than 50 considered low, between 50-80 as moderate and above 80 as high.[117]

4.3.3.4 Healthy Food Diversity Scoring

Healthy Food Diversity scores were calculated for each day and averaged over the number of days provided in the food record, using two separate variables: Berry index and health value.[118] Berry index measures diet diversity, generating a score between 0 and 1-1/n.[118] With the Berry index, a value of 0 indicates only one food item is being consumed. Scores closer to 1indicate an equal distribution of different foods. Health value is used to rank the health benefit of foods, with healthier foods having higher health factors.[118] Within each of these groups, foods recommended to be chosen most often in Canada's Food Guide are given higher health factors. The value of HFD is that a diet must include both good diet diversity and consist of healthy

foods to produce a high score.[118] In this score unhealthy foods are not omitted, and the score is able to pick up diet diversity equally for both healthy and unhealthy foods. We considered scores between 0-0.5 as low, between 0.5-0.8 as moderate and above 0.8 as high.

4.3.3.2 Quantification of processed food intake

To assess intake of processed foods, we assigned each food item a Nova category.[84] Nova is system for categorizing food by level of processing, such that category 1 is unprocessed or minimally processed, category 2 is processed culinary ingredients, category 3 is processed foods and category 4 are ultra-processed foods.[124] We calculated the amount of energy contributed by each Nova category by summing the energy from each food item. We then calculated the percent of energy from each Nova category.

4.3.3.3 Consumption of high and low potassium foods

To gain greater insight into consumption of foods traditionally considered high or low potassium, we used a provincial (Alberta, Canada) clinical renal resource.[125] This guideline classifies fruits, vegetables and grains as either high or low potassium. Each fruit, vegetable or grain product was coded as either high or low potassium based on this resource.

4.3.3.4 Serum Potassium, Hyperkalemic Events and CVD Risk Factors

Blood samples were collected at annual visits and were analyzed for C-reactive protein (CRP), lipid panel (total cholesterol (TC), LDL, HDL and triglycerides (TG)), serum creatinine, and HbA_{1c}, in addition to other routine blood work. Kidney function was assessed by eGFR calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation in accordance with standard procedures in the provincial lab. All lab work was done according to standard methodology for the Alberta Health Services Core Laboratory.

To assess serum potassium, all potassium values in patients' electronic charts were reviewed and an annual mean potassium value was calculated. Values between 3.5-5.0mmol/L were considered normal in accordance with the local lab reference range. If a participant had a value outside of this range they were flagged as having a hypo or hyperkalemic event for that year.

4.3.3.5 Health Related Quality of Life and Depression

To assess health related quality of life, the 36 question Short-Form (SF-36) [126] (http://www.qualitymetric.com License Number QM047187 OPTUMInsight^{TDM}) and the Major Depressive Inventory (MDI) tools [127] were used.

4.3.3.6 Statistical Analysis

Data analysis was completed using SAS 9.0 statistical software (SAS, Version 9.4; SAS Institute Inc., Cary, NC, USA). Descriptive data are reported as mean ± standard deviation, median (interquartile range (IQR)) or percentage of total population, as appropriate. The Shapiro-Wilk test was conducted to assess the normality of distribution. Repeated measures analysis of variance was performed to assess the effects of time on primary outcomes (MDS). Univariate and multivariate linear regressions were conducted to assess potential relationships between primary outcomes of interest (potassium in the diet, MDS, HRQOL and MDI). Analysis of co-variance was performed to adjust for any variables (e.g age, sex, CKD stage) influencing primary outcomes. Chi-square tests were used to measure differences in categorical data (CKD stage, hyperkalemic events, adherence to MDS). To assess the relationship between MDS and CKD stage, we sorted the data into two groups – Stage 1-2 CKD and Stage 3-5 CKD. Diets were sorted for potassium intake under and over 2000mg per day and per 1000 kcal to assess the relationship between MDS and potassium intake. p-value$\leq$0.05 was indicative of statistical significance. Analysis was completed per protocol such that when there was data it was included,

and when data was missing (either due to a missed follow up visit or death) the sample size was smaller.

To assess for correlation between continuous variable a two-tailed Pearson's correlation was used. To assess for correlation between ordinal variable a two-tailed Spearman's correlation was used. We considered correlation r-value of less than ±0.3 a small effect, between ±0.3 to ±0.5, a medium effect and above ±0.5 a large effect.[128] To assess for the effect of time on diet quality score a one-way analysis of variance test was conducted.

4.4 Results

4.4.1 Baseline Characteristics and Participant Follow Up

Table 4.1 summarizes baseline patient characteristics. Not all participants attended every year, 10 participants had six visits, 27 had three to five visits and 13 had two visits. There were no differences between those who attended 3 to 6 visits (for age, BMI, HbA_{1c}, all $p>0.05$). Participants who attended two visits had lower body weights and a trend toward a higher eGFR ($p=0.08$) then those who attended more. Five participants died during the study: two of acute renal failure, one of congestive heart failure, one with an upper GI bleed and one of colon malignancy.

4.4.2 Misreporting

Twenty-one (11.8%) and eight (4.5%) of food records were considered under and over reported, respectively. Misreporting was not different between years (baseline 18%, year one 14%, year two 17%, year three 21%, year four 4% and year five 18%, $p=0.74$). Mis-reporters tended to misreport each year. Accurate reporting did not impact energy adjusted MDS, medians of 3.5, 4 and 4 ($p=0.8$) for over, under and accurate reporters, respectively. As misreporting did not impact MDS, all scores were included in the analysis.

Table 4.1: Patient Demographics at Baseline

Variable	Total (n=50)	Low MDS (n=8)	Moderate MDS (n=30)	High MDS (n=12)	p-value
Number of F/U visits attended	3.0 (2.3 – 5)	3.5 (2 - 5.3)	4.0 (3.0 – 5.0)	3.0 (2 – 3.5)	0.26
Male, n (%)	34 (68%)	8 (100%)	20 (67%)	6 (50%)	0.76
Age, years	65.4 (60.3 - 69.4)	62.9 (59.4 - 65.2)	65.4 (60.8 - 69.5)	67.5 (61.6 - 70.0)	0.08
Weight, kg	92.0 (81.0 - 107.9)	96.9[a] (88.9 - 110.3)	97.6[a] (84.6 - 109.7)	83.0[b] (77.2 - 86.7)	0.003
Height, m	1.7 (1.6 - 1.7)	1.7 (1.7 - 1.8)	1.7 (1.7 - 1.8)	1.6 (1.5 - 1.7)	0.24
BMI, kg/m^2	32.9 (28.4 - 37.3)	33.0[a] (29.7 - 34.5)	34.8[a] (29.1 - 37.8)	30.9[b] (28.0 - 33.6)	0.007
Energy Intake,kcal	1707 (1395 – 2165)	2090 (1859 – 2344)	1570 (1343 – 2165)	1725 (1339 – 1938))	0.24
Adequate Reporters, n (%)	41 (82%)	7[a] (88%)	23[b] (77%)	11[a,b] (92%)	0.04
Potassium Intake, mg	2429 (2039 – 3131)	2217[a] (1712 – 3403)	2429[b] (2099 – 2965)	2666[b] (2053 – 3199)	0.007
Sodium Intake, mg	2301 (1663 – 3221)	3772 (2435 – 5092)	2288 (1697 – 3152)	1932 (1495 – 2506)	0.64
Baseline Health Status					
Duration of diabetes, years	12.5 (9.3 - 22.8)	18.0 (11.8 - 28.3)	13.5 (10.0 - 21.5)	10.0 (8.8 - 14.0)	0.07
Comorbidities	5.5 (4.0 – 6.0)	4.0 (3.8 - 4.5)	6.0 (3.0 – 7.0)	5.0 (4.0 – 6.0)	0.16
eGFR, ml min^{-1} $1.73m^{-2}$	54 (27 – 83)	36[a] (30 – 56)	57[a,b] (25 – 87)	75[b,c] (39 – 85)	0.02
CKD Stage 3-5, n (%)	27 (54%)	6 (75%)	16 (53%)	5 (42%)	0.06
HbA_{1c}, mmol/mol (%)	56 (50 – 66) (7.3 (6.7 - 8.2))	56 (54 – 61) (7.3 (7.1 - 7.7))	55 (46-65) (7.2 (6.4 - 8.1))	55 (52-67) (7.2 (6.9 - 8.3))	0.86
Serum K (mmol/L)	4.6 (4.3 - 4.8)	4.6 (4.4 - 4.7)	4.6 (4.2 - 4.9)	4.6 (4.4 - 4.8)	0.09
Baseline Medication Intake					
Total number DM meds	2.0 (1.0 - 3.0)	1.5 (1.0 - 2.5)	2.0 (1.0 - 3.0)	2.5 (1.0 – 3.0)	0.07
On Insulin therapy, n (%)	33 (66%)	6 (75%)	19 (63%)	8 (67%)	0.24
Total number of BP meds	2.0 (1.0 - 3.0)	2.5 (1.8 - 3.0)	2.0 (1.0 - 3.8)	2.0 (2.0 - 2.3)	0.09

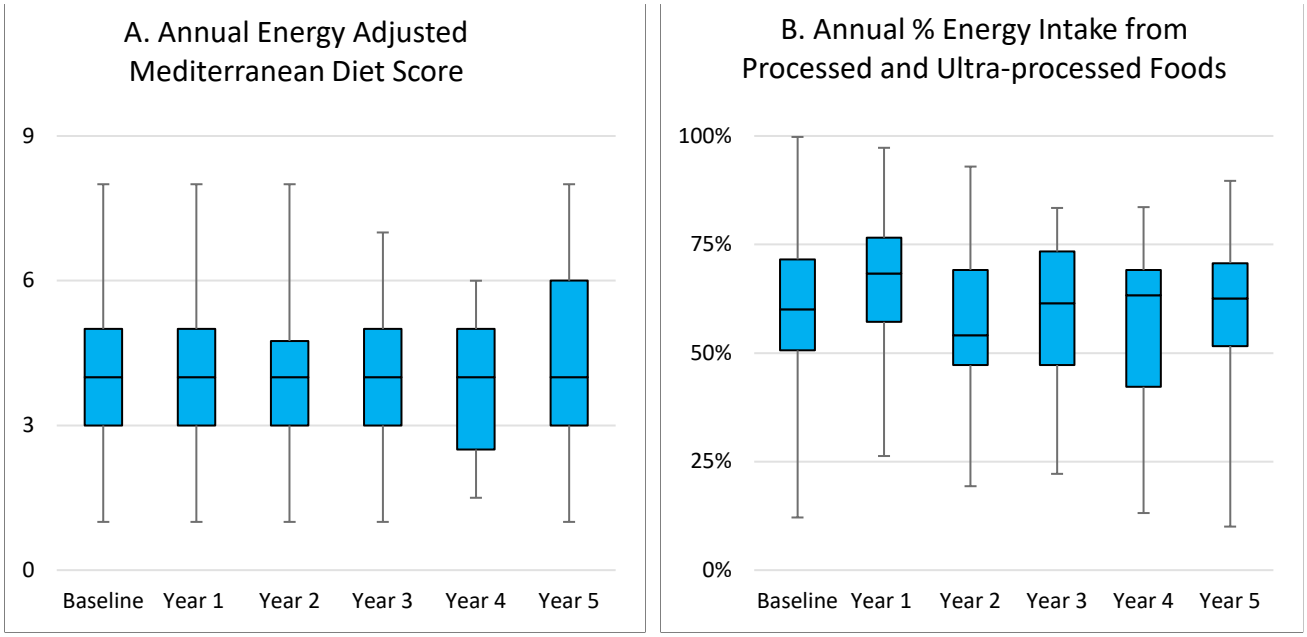
On RAASi, n (%)	40 (80%)	8 (100%)	23 (77%)	9 (75%)	0.47
On Loop or Thiazide Diuretics, n (%)	33 (66%)	5 (63%)	20 (67%)	8 (67%)	0.69
On statin therapy, n (%)	44 (88%)	6 (75%)	27 (90%)	11 (92%)	0.11
Total number of medication	8 (7 – 10)	9 (7 - 10)	8 (7 - 12)	7 (7 – 8)	0.872
Total number of natural health products	2 (1 - 4)	1^{a} (1 - 3)	2^{b} (1 - 4)	2^{b}(1 – 4)	0.04

Data are presented as median (IQR) unless otherwise specified. MDS score categorization based on energy adjusted scoring (g per 1000kcal), with Low MDS scores between 0-2, Moderate MDS scores between 3-5 and High MDS scores 6 and above. Stage 3-5 CKD considered as all participants with an eGFR less than 60 ml min^{-1} $1.73m^{-2}$.
[1]Legend: Comorbidities - number of diagnosed health conditions other than diabetes, CKD – chronic kidney disease, K – potassium, DM – diabetes mellitus, BP – blood pressure, RAASi – Renin Aldosterone Angiotensin System Inhibitor, Natural Health Products – includes vitamins, minerals and other nutrition supplements. Variables with different superscripts are significantly different at $p<0.05$.

4.4.3 Dietary intakes and changes over time

Diet quality, macro and micronutrient intake at baseline and follow up are presented in **Appendix I**. Dairy and fat intake both had a statistically significant trend toward reduced consumption. Carbohydrate intake was variable with statistical differences between years, however no specific trend was demonstrated. Several nutrients fluctuated in reported amount from year to year, though these fluctuations were not statistically significant, nor was there a clear upward or downward trend. Thirty-four of 50 participants with repeated measures for potassium intake changed tertiles for reported energy-adjusted potassium intake. The majority of MDS was low or moderate. However, diet quality did not deteriorate during follow up, but was stable (**Figure 4.2**). The largest portion of energy intake was made up of processed food and this was also stable (**Figure 4.2**).

Figure 4.2. Annual MDS and intake of processed foods at baseline and during follow up.



The mean MDS is considered moderate. For Nova, over 50% of energy consumed was from processed or ultra-processed foods (categories 3 and 4). Lower error bars represent minimum value. Upper error bars represent maximum value. Bottom box represents first quartile. Middle of box represents the median, top box represents third quartile. Baseline n=50, year 1 n=37, year 2 n=22, year 3 n=19, year 4 n=23, year 5 n=27.

4.4.4 Relationships to cardiometabolic risk factors

Stage 1-2 vs Stage 3-5 CKD was associated with higher MDS. During years when eGFR decreased by more than 20%, the mean MDS was 3.9 ± 1.4, with a mean change of -0.6 ± 1.8. This was lower than years when eGFR was stable with a mean MDS of 4.3 ± 1.4 and a mean change 0.1 ± 2.0. However, there was no difference in MDS scores between those who had a decline event and those who did not (4.1 ± 1.8 vs 4.1 ± 1.5, $p>0.05$). There was a statistically significant relationship between BMI and MDS at baseline, with those with higher MDS scores having lower BMIs than those with moderate or low MDS (**Table 4.1**), though this trend did not continue during follow up (number not shown). No other associations between diet quality and HbA_{1c}, TG, LDL or HDL were found (**Table 4.2**). Cardiometabolic risk factors, including eGFR, did not change over time (all $p>0.05$, data not shown).

Table 4.2: Cardiometabolic Risk Factors by Mediterranean Diet Scores

Variable	Total (n=178)	Low MDS (n=33)	Moderate MDS (n=110)	High MDS (n=35)	p-value
HbA_{1c} (%)	7.3 (6.7 - 8.1)	7.5 (7.0 - 8.2)	7.2 (6.7 - 8.1)	7.3 (6.7 - 7.9)	0.43
eGFR (ml/min/1.73m^2)	47 (24 – 76)	34 (24 - 73)	44 (22 – 73)	58 (29.5 – 85)	0.03
CKD Stage 3-5 (n, %)	109 (61%)	21 (64%)	68 (62%)	18 (51%)	0.09
Serum K (mmol/L)	4.6 (4.3 - 4.9)	4.7 (4.4 - 4.9)	4.6 (4.2 - 4.9)	4.6 (4.3 - 4.9)	0.88
Total-C (mmol/L)	3.6 (2.9 - 4.5)	3.8 (2.9 - 4.8)	3.6 (3.0 - 4.5)	3.6 (3.0 - 4.8)	0.72
LDL (mmol/L)	1.4 (1.1 - 1.9)	1.6 (1.0 - 1.9)	1.4 (0.9 - 1.9)	1.5 (1.2 - 1.7)	0.96
HDL (mmol/L)	1.0 (0.9 - 1.3)	1.1 (0.9 - 1.4)	1.0 (0.9 - 1.1)	1.1 (0.8 - 1.5)	0.82
TG mmol/L)	1.9 (1.2 - 3.4)	1.7 (0.9 - 2.4)	2.2 (1.3 - 3.6)	1.6 (1.1 - 3.2)	0.29
CRP (mmol/L)	2.1 (0.9 – 5.0)	2.5 (0.9 - 7.1)	2.1 (0.8 - 4.9)	1.6 (0.9 - 4.8)	0.95

Data presented as median (IQR). Results for all participants all years organized by annual MDS score with low MDS 0-2, moderate MDS 3-5, high MDS 6-9. Stage 3-5 CKD – eGFR less than 60 ml min^{-1} 1.73m^{-2} Legend: MDS – Mediterranean diet score, CKD – chronic kidney disease, K - potassium, Total-C - total cholesterol, TG – triglycerides, CRP - C-reactive protein

4.4.5 Relationships of diet quality to potassium (dietary, serum, hyperkalemia)

Dietary potassium intake above 2000mg vs below 2000mg was associated with higher energy adjusted MDS (mean 4.3 ± 1.6 vs 3.6 ± 1.5, $p<0.01$, $r^2=0.10$). There was no association between dietary potassium intake and serum potassium levels. Of the 50 participants, 9 had hyperkalemia. Five participants had hyperkalemia once, four had hyperkalemia more than once, for a total of 15 events. Those who had hyperkalemia had worse kidney function, consumed less potassium, had lower diet quality and less frequently reported consuming high potassium fruits, vegetables or grains compared to those who did not have hyperkalemia (**Table 4.3**). As CKD Stage increased, there was no difference in consumption of low potassium grains, fruits or

vegetables, however there was a decreasing trend in consumption of high potassium grains and fruits, but not vegetables.

Under reporters had lower potassium intakes compared to accurate and over reporters (1502g ± 476 vs 2464g ± 864 vs 3242g ± 1083; $p<0.05$). However, there was no relationship between hyperkalemia and misreporting (1 hyper- and 1 hypo- kalemic event in the over-reporters; 3 hyper- and 0 hypo- kalemic events in the under-reporters; 11 hyper- and 3 hypo-kalemic events in the adequate reporters; $p=0.90$ and $p=0.12$, respectively). To account for differences in reported potassium intake, we used energy adjusted potassium intake (per 1000kcal) and included all data in the final analysis. There was no relationship between energy adjusted potassium intake and hypokalemic events (3 below the median vs 1 above the median, $p>0.05$).

The impact of medications on outcomes was examined. There was no relationship between hyperkalemia and the use of potassium sparing diuretics (hyperkalemia: 2 out of 33 (6.1%) vs no hyperkalemia: 2 out of 122 (1.6%), $p=0.32$). However, those who experienced hyperkalemia were more likely to use loop or thiazide diuretics (28 out of 33 (84.8%) vs 65 out of 122 (53.3%), $p=0.02$). There was no relationship between hypo or hyperkalemic events and the use of renin angiotensin aldosterone system inhibitors.

Table 4.3: Characteristics of participants who did vs did not experience a hyperkalemic event

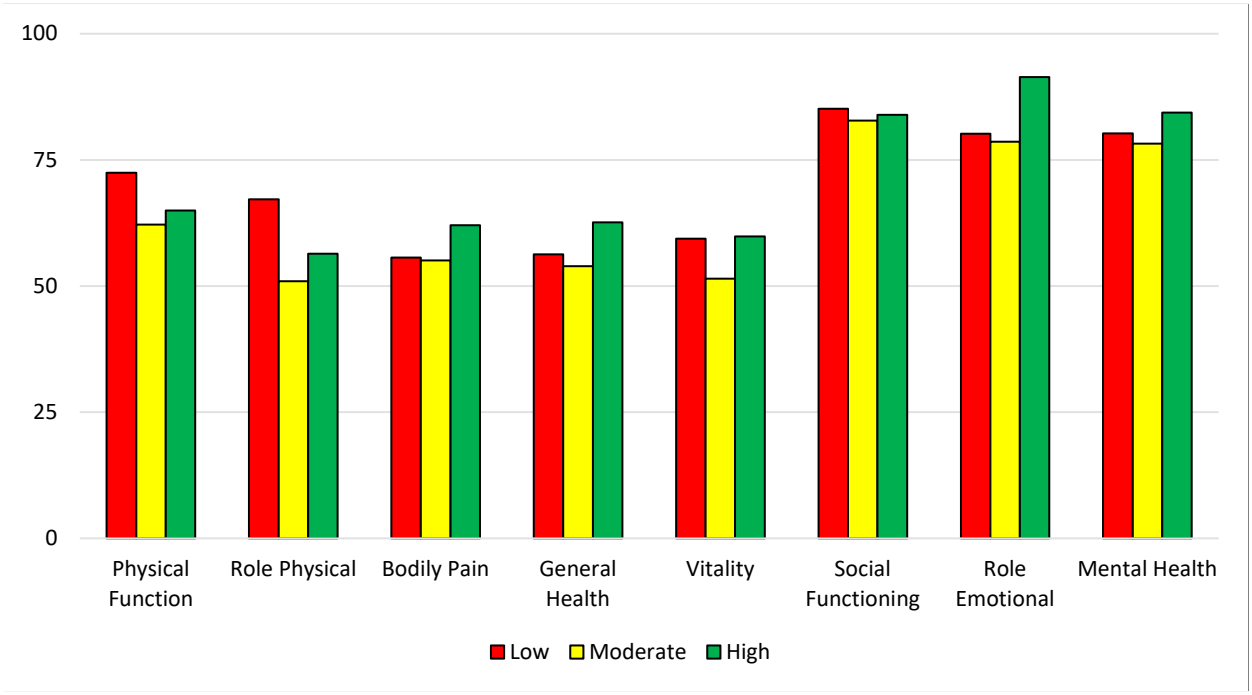
Indicator	Had hyperkalemic event (n=9 participants, 33 records,15 hyperkalemic events)	Did not have a hyperkalemic event (n=41 participants, 122 records)	p-value
Demographics and Descriptions			
Potassium Intake, mg	1505 (1250 – 1983)	2478 (2030 – 2974)	<0.001
Energy Intake, KJ (kcal)	5142 (3920 – 6949) (1229 (937 – 1661))	6920 (5803 – 8318) (1654 (1387 – 1988))	0.13
Potassium Intake/1000kcal	1257 (859 – 1574)	1495 (1291 – 1791)	0.0042
Serum potassium	5.2 (4.9 - 5.4)	4.5 (4.2 - 4.8)	<0.001
eGFR, ml min^{-1} $1.73m^{-2}$	26 (21 – 30)	55 (25 – 84)	0.002
Stage 3-5 CKD, n (%)	33 (100%)	66 (54.1%)	0.001
Age	67.4 (64.4 - 70.5)	68.8 (62.0 - 73.8)	0.13
BMI	25.7 (22.8 - 36.8)	32.6 (27.0 - 36.4)	0.13
Mediterranean Diet Scores			
Raw MDS	3 (3 – 4)	4 (3 – 5)	0.03
Energy Adjusted MDS	4 (2 – 5)	4 (3 – 5)	0.09
Energy Adjusted MDS (Davis)	2 (1 – 3)	2 (2 – 3)	0.19
% Energy Intake of Minimally Processed, Processed and Ultra-Processed Foods			
Nova 1	27.6% (14.6 - 46.2)	34.9% (25.8 - 45.9)	0.51
Nova 2	1.4% (0.0 – 6.2)	1.2% (0.0 - 4.6)	0.92
Nova 3	4.3% (0.1 – 10.2)	5.5% (0.2 – 12.4)	0.10
Nova 4	62.3% (41.1 – 73.5)	50.4% (40.6 - 64.2)	0.19
Was consumption of low potassium foods reported?			
Low Potassium Grains, n (%)	30 (90.9%)	113 (92.6%)	0.89
Low Potassium Fruits, n (%)	22 (66.7%)	89 (72.9%)	0.88
Low Potassium Vegetables, n (%)	26 (78.8%)	111 (91.0%)	0.003
Was consumption of high potassium foods reported?			
High Potassium Grains, n (%)	21 (63.6%)	97 (79.5%)	0.16
High Potassium Fruits, n (%)	4 (12.1%)	59 (48.4%)	0.01
High Potassium Vegetables, n (%)	8 (24.2%)	55 (45.1%)	0.14

Data are presented as median (IQR) unless otherwise specified. Hyperkalemic event defined as any serum potassium level about 5.0mmol/L (in accordance with reference range as provided by provincial lab). Stage 3-5 CKD defined as participants with an eGFR less than 60 ml min^{-1} $1.73m^{-2}$. mg – milligram, CKD – chronic kidney disease, Raw MDS – Mediterranean Diet scores, not adjusted for energy intake, Energy Adjusted MDS – Mediterranean Diet scores adjusted for energy intake, Nova – (not an acronym) is a standardized way to describe level of food processing with group 1 described unprocessed or minimally processed foods, group 2 processed culinary ingredients, group 3 processed foods and group 4 ultra-processed foods.

4.4.6 Relationships to HRQOL and Depression

HRQOL was below Canadian normative data [21], but stable during follow up. High vs low MDS was associated with improved HRQOL (mental health 84.4 ± 14.3 vs 80.3 ± 17.1, $p<0.05$; general health 62.6 ± 21.0 vs 56.3 ± 19.8, $p<0.001$) (**Figure 4.3**). There was no statistically significant difference between MDS and the other six subdomains. High vs low MDS was also associated with fewer depressive symptoms (9.1 ± 7.4 vs 11.7 ± 10.6, $p=0.01$).

Figure 4.3: The association between Mediterranean Diet Score (MDS) and Health Related Quality of Life (HRQOL)



Low MDS (score between 0-2), n=33; Moderate MDS (score between 3-5), n=110; High MDS (score 6 and above), n = 35

4.4.7 The correlation of diet quality scores with nutrient intake

For all diet quality tools, as scores increased, fibre, MUFA:SFA ratio and vitamin C intake increased while saturated fat and energy density decreased. HFD had the highest correlation co-efficients for vitamins and minerals (**Table 4.4**). HEI had the highest correlation co-efficients for macronutrients and servings of foods from food groups. Overall, the strength of correlations were considered weak.

Table 4.4: Correlation of Diet Quality Metrics with Nutrients

Nutrient	Healthy Eating Index	Healthy Food Diversity	MDS
Macronutrients			
Energy density (kcal/g)	-0.373**	-0.373**	-0.264**
% Energy from Carbohydrates	0.412**	0.159*	0.215**
% Energy from Protein	0.188*	0.212**	0.154*
% Energy from Fat	-0.486**	-0.175*	-0.239**
% Energy from Saturated Fat	-0.518**	-0.254**	-0.305**
MUFA:PUFA	0.174*	0.243**	0.278**
Fiber (g/1000kcal)	0.499**	0.506**	0.375**
Average macronutrient correlation value[1]	0.379	0.275	0.261
Micronutrients			
Calcium (mg/1000kcal)	0.430**	0.195**	-0.158*
Phosphorus (mg/1000kcal)	0.365**	0.247**	0.050
Sodium (mg/1000kcal)	-0.030	-0.100	-0.130
Potassium (mg/1000kcal)	0.571**	0.657**	0.371**
Vitamin A (mcg/1000kcal)	0.060	0.229**	0.090
Thiamine (mg/1000kcal)	0.291**	0.368**	0.198**
Riboflavin (mg/1000kcal)	0.170*	0.148*	-0.090
Niacin (mg/1000kcal)	0.130	0.269**	0.207**
Vitamin B6 (mg/1000kcal)	0.355**	0.536**	0.367**
Vitamin B12 (mcg/1000kcal)	0.000	0.110	0.030
Vitamin C (mg/1000kcal)	0.376**	0.428**	0.302**
Vitamin D (mcg/1000kcal)	0.174*	0.209**	0.050
Average micronutrient correlation value[1]	0.246	0.291	0.170
Servings of from each food group			
Grain Products	0.057	-0.305**	-0.164*
Vegetable and fruit	0.609**	0.545**	0.356**
Milk & Alternatives	0.378**	0.022	-0.259**
Meat & Alternatives	-0.003	-0.021	0.005
Average food group servings correlation value[1]	0.262	0.223	0.196

n=178; ** Correlation coefficient is significant at $p \leq 0.01$ level (2-tailed). * Correlation coefficient is significant at $p \leq 0.05$ level (2-tailed). Displaying r-values using two-tailed Pearson's Correlation. [1] Average r-value calculated for each subcategory, using the natural number r-value such that only the r-strength as opposed to the r-direction is captured.

With regards to nutrients of interest to the CKD population, both HEI and HFD were moderately correlated with potassium (r-value 0.571 and 0.657 respectively, both $p<0.01$). Only a low HEI score was associated with potassium intakes below the recommended 2000mg limit for a low potassium diet (5). All other diet quality scores were associated with intakes above 2000mg of potassium but below the adequate intake (AI) of 4700mg. Phosphorus was weakly associated with HEI (r-value 0.365, p-value <0.01). A high MDS and a low HEI score were associated with phosphorus intakes below the recommended 1000mg limit for a low phosphorus diet (5). Only the high MDS category was below the recommended daily allowance (RDA) of 700mg. All others were associated with intakes above 1000mg of phosphorus.

With regards to intake from different food groups, vegetable and fruit consumption showed the highest correlation to diet quality (**Table 4.2**). While not many participants achieved a high diet quality score, for those with a high HEI score (n=7), all participants met the RDA for vitamin C and B6, while 60% met the RDA for vitamin A. For those with a high MDS (n=5), all participants met the RDA for vitamin C, 80% for vitamin B6 but only 20% for vitamin A. Across all diet quality tools there was a lower percentage of participants meeting the RDA when scores were considered low or moderate.

4.5 Discussion

The relationship between Mediterranean style diets on health outcomes in patients living with diabetes and CKD is not well known. In the first analysis, our goal was to understand the association between Mediterranean-style diets and health outcomes (including glycemic control, lipids, CKD stage, hyperkalemia and health related quality of life) among patients with diabetic

kidney disease. Traditional diet therapy for patients with CKD has focused on management of electrolyte levels and reduced protein intake more so than diet quality.[129] This has led to a growing concern that potassium restricted diets may prevent patients from consuming foods that are otherwise considered healthy and associated with lower cardiovascular risk in the general population.[11,20,87]

4.5.1 Mediterranean Diet Scores and Health Outcomes

We found that adherence to Mediterranean style diets was predominately moderate or low. This is consistent with other studies, reporting low diet quality in the CKD population.[103,116] Low diet quality in this population is a concern, as a recent meta-analysis showed that healthy diet patterns (including MDS) in patients with CKD was associated with reduced mortality.[130] Interestingly, this same meta-analysis reported finding no articles reporting on CKD and diet quality for the outcomes of cardiovascular related deaths, hyperkalemia or lipids.[130]

Patients with CKD are at high risk of hyperkalemia [12], hyperkalemia is associated with increased mortality, in part due to fatal cardiac arrythmias.[74] Healthy diets tend to contain more potassium [3] as foods which improve diet quality, such as whole grains, fruits and vegetables, are considered high potassium foods.[131] However, it is worth noting, that dairy products, animal proteins and beverages also tend to be significant contributors of dietary potassium intake.[132,133] In our study we found that those with better diet quality consumed more potassium than those with poor diet quality but did not have higher rates of hyperkalemia or higher serum potassium levels. Lack of correlation between potassium from whole foods and serum levels has been previously demonstrated.[134,135] It has been proposed that the lower bioavailability of potassium in unprocessed and minimally processed foods, when plant cell walls are intact, could be

blunting the effect on serum potassium levels.[60] Additionally, it has been proposed the base-inducing foods (plant foods) tend to shift potassium intra-cellularly minimizing impacts on serum levels.[11] This may be particularly relevant for patients living with both CKD and diabetes, as these patients are at high risk of cardiovascular events and Mediterranean diets have been associated with improved cardiovascular outcomes.[109,110]

We found that the majority of energy intake came from processed and ultra-processed foods, with those with Stage 3-5 CKD consuming more than Stage 1-2 CKD. As CKD progresses, the risk for hyperkalemia increases [12] and so does the likelihood that low potassium diets will be recommended. While another study, in Brazil[103], reported on processed food intake among patients with CKD, this is the first study, that we know of that has investigated processed food intake in the Canadian CKD population. The importance of understanding processed food intake is relevant as there is growing concern that potassium additives in processed food can significantly increase potassium intake.[11] This is coupled with a concern that potassium content from potassium additives in processed foods is not well established.[113] As the intake of processed food was high, this may suggest that, patient teaching materials for potassium management would benefit from including information on how to avoid potassium in ultra-processed foods.

More advanced CKD was associated with lower diet quality. While a cause-and-effect relationship cannot be elucidated, a bi-directional relationship is possible. Those with poor diet quality may be more likely to develop CKD as poor diet quality is associated with CKD risk factors (diabetes[136] and CVD [137-139]). And, those with advanced CKD may experience more barriers to healthy eating, including (but not limited to), restrictive diet recommendations[11], fatigue[140] and financial burden.[141] While we did not explicitly ask participants about the diet

advice they had received, it was notable that as CKD stage increased, consumption of high potassium grains and fruits decreased. It is possible that patients being advised to lower their potassium intake through restriction of these foods was one reason for decreasing diet quality and is an area for further research.

Higher MDS was associated with lower BMI scores at baseline, though this trend did not continue through follow up. The relationship between BMI and disease outcomes in CKD is particularly nuanced [142] and this may, in part explain, why the relationship with MDS and BMI is not clear from our study. There is evidence that higher BMIs can be protective in advanced CKD, in part due to significant risk for malnutrition as CKD progresses.[142] As low MDS was associated with worse CKD, a lower BMI in this population, may in part be related to increased uremic symptoms or malnutrition in this cohort. Ultimately, more longitudinal studies investigating diet quality, nutritional status and CKD are warranted. With regards to diet quality and other cardiometabolic risk factors (lipids, glycemic control), it is quite possible that medication management was a confounder, as the majority of our participants were taking several medications to manage cardiometabolic risk factors.

A novel finding was the relationship between diet quality and health related quality of life, such that those with better diet quality benefited from higher scores in mental and general health. While studies in other populations have found similar findings, this is the first study, to our knowledge, that has specifically examined this outcome in patients with CKD. Although we cannot infer causality from this association, it is worth noting, that two separate intervention trials, in the metabolic syndrome population [143] and another investigating participants with depressive symptoms [144] found that Mediterranean diets improved HRQOL scores.

With regards to how food intake changed over time, we found a statistically significant trend for reduced dairy consumption throughout the follow up years. Reduced dairy consumption may have been related to nutrition counselling for patients with kidney disease as dairy is high in both potassium and phosphorous and is frequently restricted. In our cohort, 68% of participants changed tertiles of potassium intake; changing tertiles for potassium intake has been previously demonstrated.[145] Engberink et al used urinary biomarker as opposed to diet records to assess potassium intake.[145] As both our study and Engberink et al, report variation, this finding may suggest that variation in our sample is not due to dietary misreporting but rather normal fluctuations in intake and highlights the importance of serial measure for understanding how dietary intake may impact health outcomes. Other nutrients and MDS also showed some fluctuations year by year but did not achieve statistical significance. That MDS did not change through follow up was a surprising finding as we had hypothesized that diet quality would deteriorate. This finding may be related to the fact that our cohort was made up of 54% late stage CKD participants who may have already made changes to their diet. Further trials that use repeated MDS that follow participants from Stage 1 CKD to ESRD are likely warranted to understand how disease progression impacts MDS.

4.5.2 Diet Quality Tools and Nutrient Adequacy

When the correlation between diet quality and nutrient adequacy was investigated, we observed that HEI and HFD were more highly correlated with nutrient intake than MDS. However, that a high HEI could be achieved without participants meeting some RDAs may raise concerns amongst dietitians using the tool to assess intakes against the RDA benchmark. Diet quality tools define beneficial and detrimental foods differently. Vegetables, fruits, whole grains and fish were considered beneficial by all 3 tools.[111,117,118] Meat and dairy are detrimental in

MDS whereas both HEI and HFD consider low fat meat and dairy beneficial.[111,117,118] Meat and dairy are both sources of highly bioavailable phosphorus.[42] For CKD patients who need to limit their phosphorus intake, moderation of these foods may be beneficial. As such, it was noted that high MDS scores were achieved with a lower intake of phosphorus compared to HEI and HFD and that only the high MDS fell below the low phosphorus limit.

With regards to nutrient intake, when diet quality scores were compared by quartiles those in the lowest quartiles consumed more saturated fat and had higher energy density, while those in the highest quartile consumed more fibre and had higher MUFA:SFA. An expected finding was that higher diet quality was associated with higher potassium and tended to exceed the recommended limits for low potassium diets. For patients requiring a potassium restriction these diet quality tools may have limited applicability. However, for adults living with earlier stages of CKD or who do not require potassium and/or phosphorus modification, diet quality tools developed for the general population may be appropriate.

4.5.3 Limitations

Our study has limitations. First, our sample was relatively homogenous with regards to diet quality. However, the use of repeated diet measures enabled us to investigate intra-participant scoring and our cohorts' stable intra-participant results improve reliability. Second, participants were recruited from a diabetic nephropathy prevention clinic where participants are regularly seen by a multi-disciplinary team, including a renal dietitian. While we did not explicitly ask patients about how frequently they were following up with this clinic, that fact that diet quality did not improve over time despite likely access to a dietitian, was expected as this has been previously reported.[116] That being said, the success of this program with regards to improvements in glycemic control, blood pressures and lipids through pharmacological

management has been previously documented and likely somewhat explains our cohort's stable cardiometabolic risk factors.[146,147]

A strength of these studies was the use of repeated 3-day food records enabling serial diet assessments. Accuracy in nutritional reporting of free-living subjects is well known to be a challenge in this field of research.[148] Serial scoring enabled an investigation of how diets change over time and increases confidence in nutrient intake estimates. Additionally, we considered nutrients and diet quality using an energy-adjusted model which can help mitigate over and under reporting of nutrient intakes.

4.6 Conclusion

In this sample of patients living with diabetes and CKD, followed over 6 years, adherence to Mediterranean diets was overall moderate, though consistent over time. MDS was not associated with serum potassium level but was associated with higher intake of both low and high potassium fruits and vegetables and high potassium grains. Those who had a hyperkalemic event consumed more processed food but MDS was the same. There was no association between MDS and cardiometabolic risk factors, however there was an association between lower MDS and lower kidney function. Higher MDS was associated with better mental and general health domains assessing HRQOL. While HEI and HFD were more correlated with nutritional adequacy, their application in the advanced CKD population may be limited due to the value placed on higher potassium intake than may be recommended. While MDS was not affected by lower phosphorus intake it was weakly correlated with nutritional adequacy. Given the specific and evolving nutrition needs of this population, development of a CKD-specific diet quality tool may be warranted. Further studies are needed to help define which healthy diet patterns in CKD are associated with improved health outcomes and nutrient adequacy.

Chapter 5: The impact of protein source on serum potassium and phosphorus levels in adults living with advanced kidney disease

5.1 Abstract

Background and Aims: Plant proteins may be restricted on low potassium/phosphorus diets. The primary objective was to investigate the impact of protein source on serum potassium and phosphate levels in adults with stage 4-5 chronic kidney disease (CKD), including hemodialysis (HD).

Methods and Results: Using a cross-sectional design, 24-hour recalls or food frequency questionnaires were used to assess dietary intake. Serum values were obtained from medical records. Quartiles (Q1-4) of plant:animal protein serving ratios was considered to investigate outcomes, with Q1 having high animal and low plant serving intake and those in Q4 having high plant and low animal servings. 216 participants were enrolled, 135 on HD and 81 stage 4/5 CKD. For both HD and CKD, there was no difference in either serum potassium or phosphate levels between those in Q4 consuming *high plant:animal* vs Q1 *low plant:animal* (for HD: potassium 4.6mmol/L vs 4.6mmol/L; phosphate 1.8mmol/L vs 1.6mmol/L, respectively; for CKD: potassium 4.7mmol/L vs 4.6mmol/L; phosphate 1.4mmol/L vs 1.4mmol/L; all $p>0.05$). Those in Q4 consuming *high plant:animal* consumed 7.5g (62%) more fibre than those in Q1 (*low plant:animal*). For diet quality, Q4 (*high plant:animal*) had a 12.8 point (24%) higher healthy eating index score than Q1 (*low plant:animal*). There was no relationship between plant:animal and serum albumin or hospital admissions (all $p>0.05$).

Conclusions: Consumption of higher proportions of plant protein was not associated with higher serum potassium or phosphate levels but was associated with higher fibre and diet quality.

5.1 Introduction

Low potassium or phosphorus diets are often recommended for adults living with chronic kidney disease (CKD) to help prevent and manage hyperkalemia or hyperphosphatemia.[20] In Canada, plant proteins (e.e. nuts, seeds, pulses) are frequently restricted on these diets.[149,150] Plant protein consumption in the general population is often encouraged, as plant proteins are considered beneficial to health.[151] Emerging evidence suggests that in the kidney population plant proteins may also be beneficial. Specifically, evidence suggests that higher plant protein intake is associated with reduced urinary urea nitrogen excretion [47], reduced risk factors for thrombosis [46], and reductions in cardiovascular risk markers.[52]

We recently conducted a literature review of plant versus animal protein source on dietary phosphorus intake and serum phosphate levels and found that protein source was not associated with changes in intake or serum levels.[152] However, we noted that in some cases, nutrition markers, such as body weight or serum albumin, were lower among those who consumed more plant than animal protein.[152] Therefore, the primary objective of this study was to investigate the impact of ratio of protein serving source (plant to animal) on serum potassium and phosphate levels and markers of nutritional and health status (serum albumin, body mass index (BMI) and hospital admissions). We hypothesized that increased high plant to animal servings will not be associated with increased serum potassium or phosphate levels, nor will it be associated with worse nutritional or health status.

5.2 Subjects and Methods

5.2.1 Study Population

Eleven kidney care clinics (CKD) and hemodialysis (HD) centers in Alberta recruited for this study. Inclusion criteria: estimated glomerular filtration rates (eGFR) less than or equal to

30mL/min/1.73m^2, age at or above 18. Exclusion criteria: unable to provide informed consent, unable to complete questionnaires (e.g. language barrier, cognitive ability) and those requiring enteral or parenteral feeds. Potential participants were advised of the study through brochures and unit staff members at scheduled visits. Written and informed consent was provided by all participants. This study was approved by the ethics research board of the University of Alberta (Pro00077347 and Pro00084546).

5.2.2 Assessment of health history and medication use

At enrollment, all participants were asked about their height, weight, number of hospital admissions in the last 12 months, phosphorus binder use and co-morbidities. Clinic of recruitment (HD or CKD) and number of years followed by the clinic was also noted. As phosphate binding capacity is unique to each type of phosphorus binder, we considered whether a participant reported being on a phosphorus binder and the total daily number of tablets. In year 2 and 3, the enrollment questionnaire also asked about education level, family income, ethnicity, all medications and natural health products routinely used.

5.2.3 Estimation of dietary intake

Dietary intake was assessed using 24 hour recalls and food frequency questionnaires. 24-hour recalls using the Automated Self-Assessment 24-hour dietary assessment tool (ASA24) was used only in year one. ASA24 is a free, web-based tool that guides participants to recall dietary intake over the last 24 hours using a multiple pass approach. The ASA has been validated against recovery biomarkers in the general population to estimate energy, protein, potassium and sodium [153,154]. Under-reporting of potassium from 24-hour recalls was reported to be 0-4% based on pooled results from five validation studies.[153] From the ASA24 output, we used energy, protein, fibre, potassium and phosphorus intake, in addition to the servings of plant proteins (legumes,

soy, nuts and seeds and whole grains) and animal proteins (meat, fish, and poultry, dairy products and eggs).

In year two and three of data collection, the dietary intake assessment tool was assessed using a food frequency questionnaire, the diet history questionnaire 3 (DHQ3) to assess diet and portion sizes over the past month. 263 foods and beverages and 26 dietary supplements. The DHQ has been validated in the general population to provide similar nutrient estimates to other comprehensive food frequency questionnaires and has been validated against recovery biomarkers.[154,155] Under-reporting of potassium from food frequency questionnaires was reported to be 5-6% based on pooled results from five validation studies.[153] From the DHQ3, we used energy, protein, fibre, potassium, and phosphorus, in addition to servings of plant proteins (legumes, soy, nuts and seeds and whole grains) and animal proteins (meat, fish, and poultry, dairy products and eggs). Additionally, the DHQ3 calculates grams of animal and plant proteins and a diet quality score using the healthy eating index (HEI) which were evaluated in our study.

For all nutrients of interest (energy, protein, potassium, phosphorus) we evaluated the total reported daily intake. Additionally, we evaluated energy and protein intake per kilogram (kg) of body weight and potassium and phosphorus intake per 4186kJ (1000kcal) of energy intake.

5.2.4 Assessment of serum potassium and phosphate levels

Results of blood samples collected as part of standard clinical care were retrieved from medical records for the 12-month period prior to dietary assessment. For HD, most blood samples are drawn at the dialysis unit before treatment. For CKD, in most cases, non-fasting blood samples are drawn at an outpatient facility every 1-3 months.

Mean serum potassium and phosphate levels were considered over a 12-month period. All lab results were reviewed for classification of either hyperkalemia or hyperphosphatemia, using the Alberta renal clinic guidelines. Alberta renal clinics define hyperkalemia as a serum potassium value above 5.5mmol/L [156] and hyperphosphatemia is defined as a serum phosphate level above 1.8mmol/L (similar to the recommended 2003 KDOQI clinical practice guideline for bone metabolism and disease in chronic kidney disease).[157] Of note, these are higher than the standard laboratory reference ranges of 3.5-5.0mmol/L and 0.7-1.5mmol/L, respectively. If a participant had any potassium or phosphorus values in the hyperkalemic or hyperphosphatemic range, they were considered to have had a hyperkalemic or hyperphosphatemic event in a dichotomous fashion (yes/no). There was some variability in the number of lab values that were available for each participant for the 12-month period of laboratory data collected, therefore percent of labs considered hyperkalemic and hyperphosphatemic were also considered by dividing the number of events by the total number of values available.

The temporality of dietary recall and lab work date was also considered, with a separate analysis of the blood value drawn closest to the questionnaire date for both serum potassium and phosphate.

5.2.5 Assessment of nutrition and health status

Serum albumin was collected as part of standard clinic blood work. Adequate protein and energy reporting was also considered. For HD, adequate protein intake was considered when total protein intake was reported to be greater than or equal to 1.2 grams per kilogram ideal body weight.[20] For CKD, adequate protein intake was a protein intake between 0.6-0.8 grams per kilogram ideal body weight.[20] Adequate energy intake was considered when reported intakes

were greater than 30 kilocalories (kcal) per kilogram ideal body weight. BMI and hospital admissions were also considered.

5.2.6 Data Analysis

Statistical analysis was completed using SPSS version 26 with a predetermined alpha of 0.05. The Gaussian natures of the variables was examined with histograms. Independent t-tests were used for normally distributed variables that contained two groups, all tests were 2-tailed. Chi-square tests were used for categorical data (such as the occurrence of a hyperkalemic or hyperphosphatemic event). Spearman's rho correlation was used to assess for correlations between continuous variables, with a predetermined value of >0.5 being considered a strong association.

The quartiles of plant to animal servings ratio was used to determine the impact of the independent variables and the dependent variables (potassium, phosphorus, energy and protein intake, serum potassium, phosphorus and albumin levels, BMI and hospital admissions). For this analysis, which contained 4-groups, a one-way analysis of variance (ANOVA) with a Games-Howell post-hoc test was used because of differences in variance between quartiles. Intake of plant to animal protein servings ratio was also plotted using scatter plots for main variables of interest (serum potassium and phosphate, dietary potassium and phosphorus intake). For those who had diet recalls completed with both the ASA24 and DHQ3, a paired t-test was used to determine differences between nutrient intake estimation by the two tools.

As blood samples analyzed in this study were drawn as part of routine clinical care, the time between the dietary recall and blood sample draws was investigated. Bland-Altman plots were used to investigate mean serum values and the serum value drawn proximate to the diet questionnaire for potassium and phosphate. The differences in date from the blood sample draw

and dietary recall were categorized into four groups: within 2 days, within 3-7 days, within 8-31 days and more than 31 days. Relationships between the proximity of blood sample date and dietary intake (mg per day), for both potassium and phosphate, were investigated using r^2 values.

5.3 Results

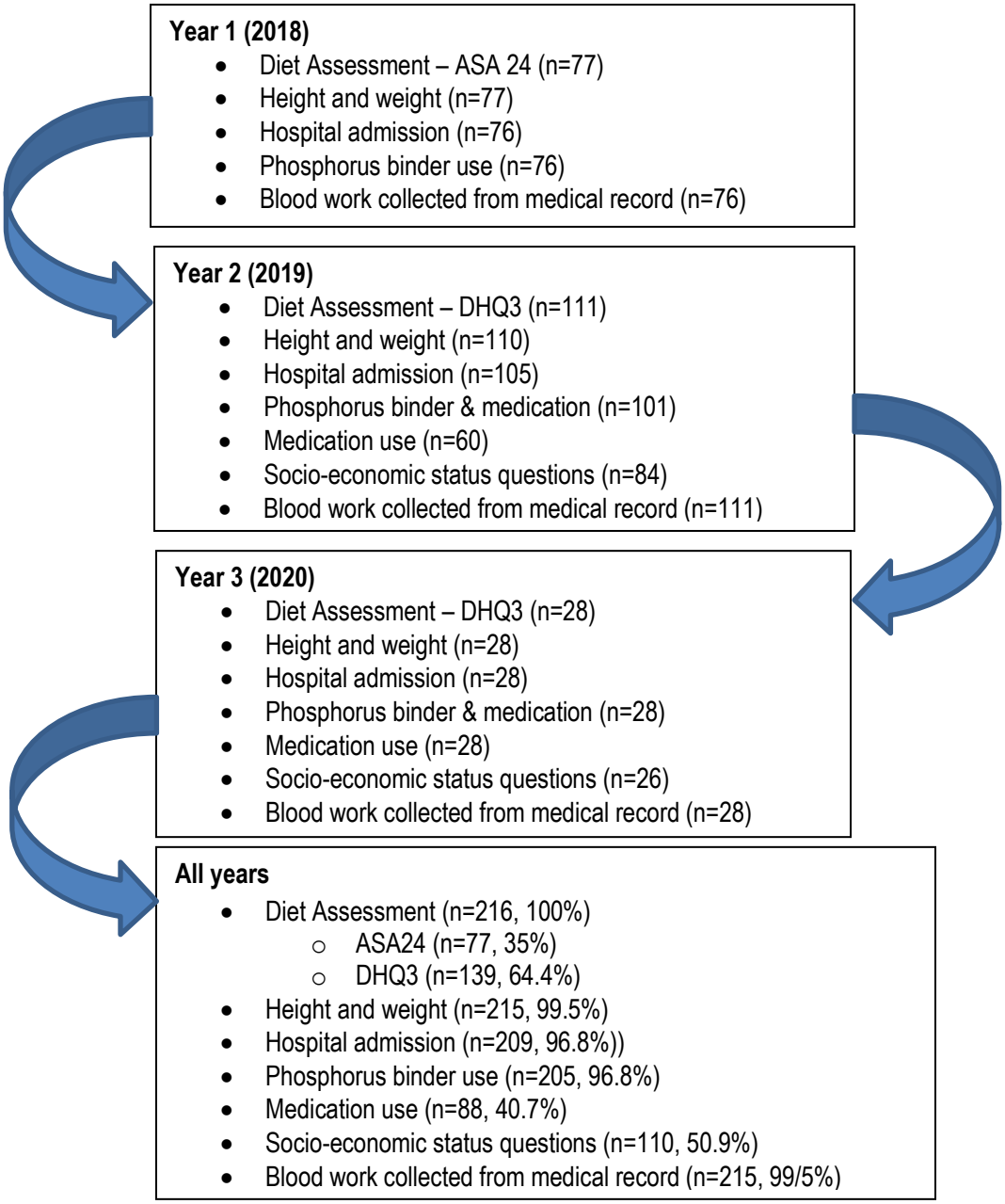
5.3.1 Nutrient assessment tools

Data collection occurred over 3 years between 2018 and 2020 with recruitment occurring between December and February of each year (**Figure 5.1**). Nutrient estimates from ASA24 and DHQ3 were comparable, therefore data from these tools was combined. Calculated sources of plant proteins (legumes, soy, nuts and seeds and whole grains) did differ between the tools, therefore the analysis used plant to animal serving ratios, as this was not different between tools. Seven individuals completed both the ASA24 and DHQ3. The estimated intake of energy, protein, phosphorus, and potassium was comparable (all $p > 0.05$).

5.3.2 Population characteristics

Participants (n=139 from year 2 and 3) who completed the expanded demographic questionnaire, most reported being married (n=77, 55.4%), having completed some post-grade school schooling (n=79, 57.7%), and identified as Caucasian (n=108, 77.7%). 110 participants answered the income question, the majority reported a low-income (under $69,000 Canadian dollars per year) (n=81, 71.8%). More males than females participated, however sex differences were not observed (**Table 5.1**). HD participants had fewer reported co-morbidities, took fewer medications (including blood pressure and diuretics) and had higher serum creatinine levels compared to CKD participants. Serum potassium and phosphate as well as nutrition and health status outcomes were reported separately for CKD and HD participants.

Figure 5.1: Study flow diagram depicting how many participants were enrolled in each year and what data was collected at each enrollment cycle.



ASA 24 – Automated self assessment for past 24 hours, DHQ3- Diet history questionnaire 3, Height, weight, hospital admissions, phosphorus binder and medication use were self-reported.

Table 5.1: Patient characteristics according to sex and clinics

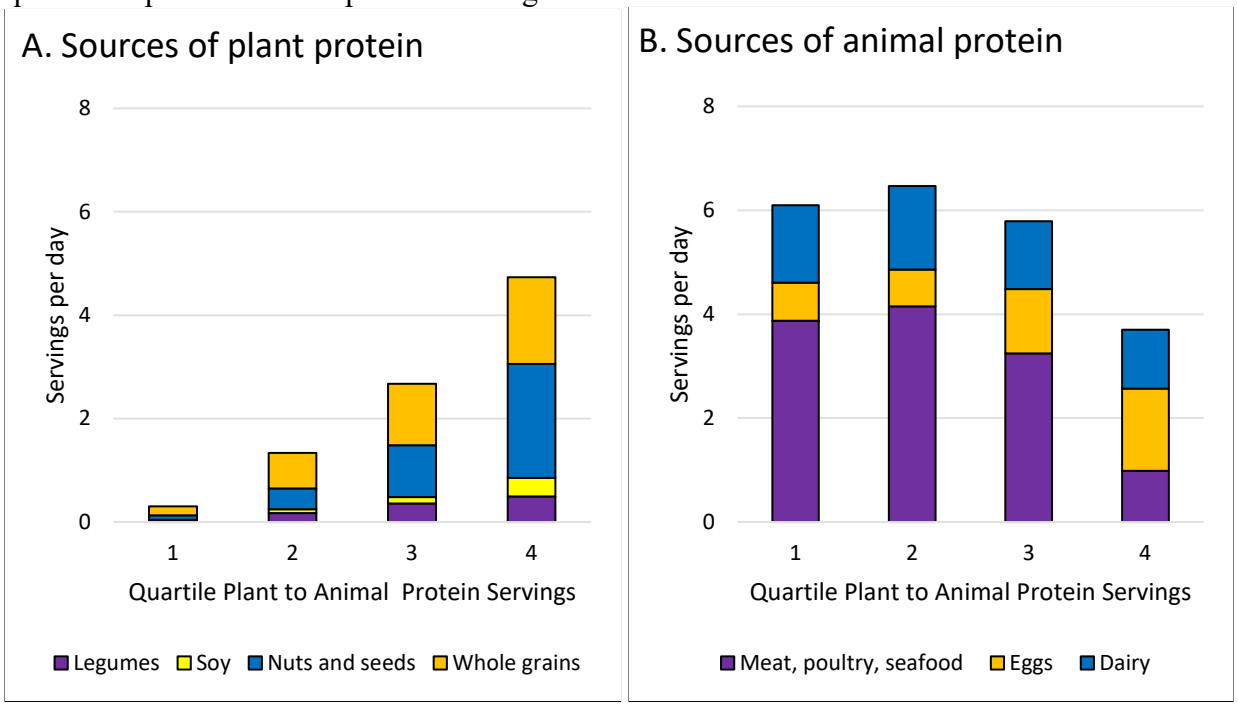
Variable	All (n=216)	Male (n=129)	Female (n=87)	p-value	CKD (n=81)	HD (n=135)	p-value
Age	65.5 (57.75-75)	65 (59-75)	65 (54-72)	0.51	66 (56-73)	64 (58-76)	0.25
BMI	27.4 (24.2-33.0)	27.5 (24.7-33.0)	25.6 (22.1-33.2)	0.36	28.0 (24.5-(32.9)	27.0 (23.4-35.7)	0.41
Number of years followed by kidney clinic	3 (1-5)	3 (1-5)	3 (1-5)	0.90	3 (1-6)	3 (1-5)	0.03
Number of co-morbidities	2 (1-4)	2 (1-3)	3 (1-5)	0.49	2 (1-5)	2 (1-4)	0.01
Number of medications	5 (2-7)	5 (3-8)	5 (2-6)	0.79	6 (4-9)	4 (2-6)	0.01
On blood pressure medications, n (%)	62 (28.7%)	41 (31.8%)	21 (24.1%)	0.48	34 (42.0%)	28 (20.7%)	<0.01
On renin angiotensin aldosterone system inhibitors, n (%)	20 (9.3%)	15 (11.6%)	5 (5.7%)	0.23	19 (23.5%)	1 (0.7%)	<0.01
On Lasix, n (%)	26 (12.0%)	17 (13.2%)	9 (10.3%)	0.51	20 (24.7%)	6 (4.4%)	<0.01
On Spironolactone, n (%)	2 (0.9%)	2 (1.6%)	0 (0.0%)	0.13	1 (1.2%)	1 (0.7%)	0.22
On insulin, (n) %	29 (13.4%)	20 (15.5%)	9 (10.3%)	0.34	11 (13.6%)	18 (13.3%)	0.33
On oral nutrition supplements, n (%)	30 (14.2%)	17 (13.3%)	13 (15.5%)	0.65	7 (9.1%)	23 (17.0%)	0.11
Number of natural health products	2 (1-3)	2 (1-3)	1.5 (1-2)	0.23	1 (1-2)	2 (1-3)	0.07
Creatinine	500 (286-781)	498 (292-781)	498 (242-774)	0.07	278 (208-354)	708 (519-833)	<0.01

Data displayed as median (interquartile ranges). P-value calculated using Student's t-test. Pre-determined alpha of 0.05 considered statistically significant. BMI – body mass index, HD – hemodialysis, CKD – stage 4-5 predialysis chronic kidney disease

5.3.3 Nutrient intake by plant to animal protein servings

The primary plant proteins were nuts and seeds. The primary animal proteins were meat, fish and poultry (**Figure 5.2**). Those who consumed the most plant proteins consumed almost five servings per day compared to those who consumed the least, reporting less than one serving. There were no significant differences between quartiles in energy, fat or carbohydrate intake (**Table 5.2**). Those consuming more plant protein consumed less protein. There were no differences in grams of animal protein intake, but there were differences in the protein source proportions.

Figure 5.2: The mean daily servings of plant (panel a) and animal (panel b) protein sources by quartile of plant to animal protein serving intake.



Quartile 4 had a high plant to animal ratio (High plant to animal) while quartile 1 had a low plant to animal ratio (Low plant to animal). High plant to animal consumed 7.5g (62%) more fibre than Low plant to animal. There were no statistically significant differences in phosphorus intake between quartiles. Low plant to animal consumed the least amount of potassium when adjusted

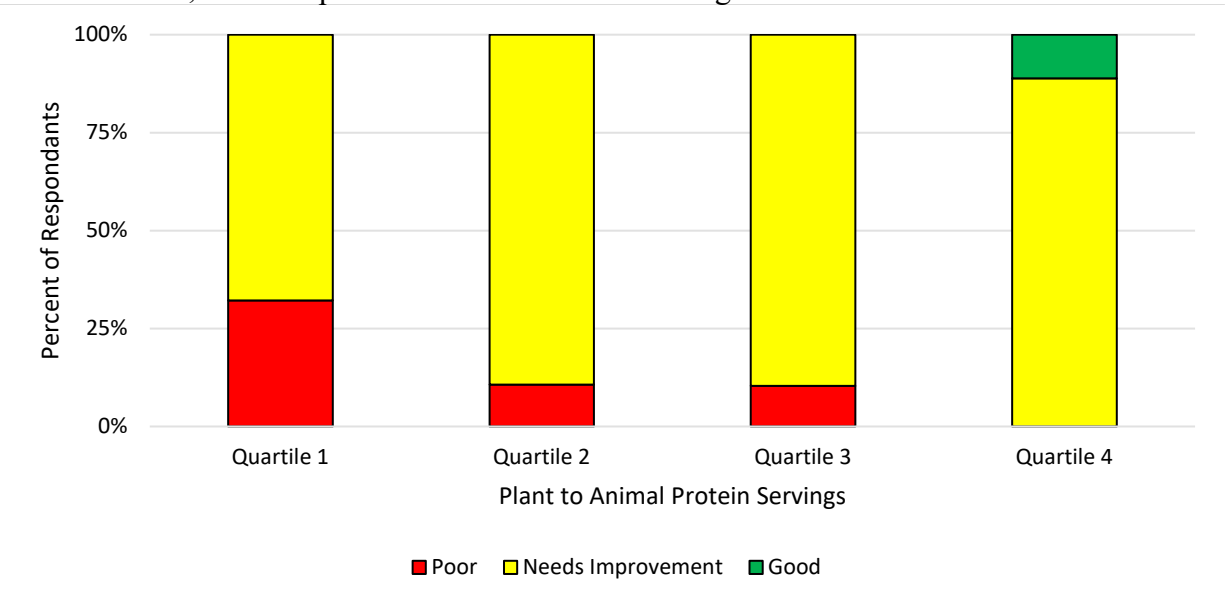
Table 5.2: Dietary intake by plant to animal protein servings ratio unadjusted for energy intake.

Group	Nutrient	Quartile 1 (0.00-0.13) (n=32, HD, 21 CKD)	Quartile 2 (0.13-0.30) (n=34 HD, 21 CKD)	Quartile 3 (0.30-0.74) (n=35 HD, 19 CKD)	Quartile 4 (0.74-2.24) (n=34 HD, 19 CKD)	p-model
Energy and Macronutrients	Energy intake (kcal/day)	1714 ± 865	1820 ± 688	1774 ± 591	1571 ± 692	0.30
	Energy intake per actual body weight (kcal/kg)	23.6 ± 13.8	25.5 ± 11.7	21.8 ± 8.5	20.9 ±10.8	0.17
	Fat (g/day)	65 ± 38	67 ± 30	69 ± 31	63 ± 38	0.80
	Carbohydrate (g/day)	213 ±119	228 ± 86	223 ± 76	200 ± 79	0.40
	Protein intake (g/day)	70 ± 36	78 ± 35	71 ± 27	59 ± 27	0.02
	Protein intake per actual body weight (g/kg)	0.97 ± 0.64	1.12 ± 0.68	0.89 ± 0.38	0.78 ± 0.55	0.01
Plant vs Animal protein	Plant Protein (servings/day)	0.33 ±0.41	1.34 ± 0.64†	2.73 ± 1.43†	4.73 ± 2.57†	<0.01
	Animal Protein (servings/day)	6.07 ± 3.61	6.47 ±3.46	5.79 ± 2.49	3.70 ± 2.48†	<0.01
	Plant protein (g/day)	15.6 ± 6.1	22.4 ± 9.0†	28.2 ± 15.4†	34.1 ± 18.2†	<0.01
	% of protein from plant protein	28.5 ± 10.4	29.5 ± 7.4	36.4 ± 5.4†	43.9 ± 9.8†	<0.01
	Animal protein (g/day)	43.4 ± 20.7	57.4 ± 30.1	49.9 ±25.0	46.1 ± 28.6	0.19
	% of protein from animal protein	71.5 ± 10.4	70.5 ± 7.4	63.6 ± 5.4†	56.1 ± 9.8†	<0.01
	Plant to animal protein ratio (g/day)	0.43 ± 0.26	0.43 ± 0.15	0.58 ± 0.14	0.87 ± 0.56†	<0.01
Micronutrients	Fibre (g/day)	12.1 ± 6.5	17.9 ± 7.2†	19.3 ± 7.8†	19.6 ± 8.2†	<0.01
	Phosphorus (mg/day)	1073 ± 556	1258 ± 525	1181 ± 447	1157 ± 513	0.25
	Phosphorus (mg/1000kcal)	636 ± 201	697 ± 147	665 ± 123	710 ± 154	0.07
	Phosphorus (mg/kg)	14.8 ± 9.2	18.2 ± 11.0	14.6 ± 6.2	14.8 ± 7.9	0.10
	Potassium (mg/day)	2062 ± 979	2628 ± 997†	2560 ± 871†	2274 ± 947	0.07
	Potassium (mg/1000kcal)	1273 ± 416	1499 ± 397†	1463 ± 313†	1487 ± 348†	<0.01
	Potassium (mg/kg)	28.5 ± 17.2	36.5 ± 15.6	31.6 ± 12.0	30.1 ± 14.7	0.04
	Sodium (mg/day)	2788 ± 1511	3121 ± 1489	3002 ± 1164	2897 ± 1370	0.30
Diet Quality	Healthy Eating Index-Score	53.4 ± 6.9	61.3 ± 8.7†	61.3 ± 7.6†	66.2 ± 9.1†	<0.01

Data displayed as mean ± standard deviation. Pre-determined alpha of 0.05 considered statistically significant. †P< 0.05 compared with Quartile 1 of plant to animal servings ratio using 1-way ANOVA with Games-Howell post-hoc test. Plant and animal protein, and healthy eating index was only calculated for those who completed the Diet History Questionnaire 3 (n=139), Quartile 1 n=21, Quartile 2 n=33, Quartile 3 n=41, Quartile 4 n=39

for energy intake compared to all other quartiles, with quartile 2, 3 and 4 being the same. For diet quality, high plant to animal had a 12.8 point (24%) higher healthy eating index score than Low plant to animal. When healthy eating index scores were grouped into "poor", "needs improvement" and "good" categories [73], it was noted that High plant to animal had no participants ranking poor, and had the only participants in the study ranking good (**Figure 5.3**).

Figure 5.3: The percentage of participants within each healthy eating index interpretation group across quartiles of plant to animal protein servings. A poor healthy eating index score is a total score under 50, needs improvement between 50-80 and good is above 80.



5.3.4 Nutrient intake by dialysis status and sex

HD participants consumed more energy and protein than CKD participants per kg body weight. There was no difference in the percent of protein intake from animal protein between HD and CKD (65.3% ± 10.6 vs 63.0% ± 8.9 p=0.20). Potassium intake was reported to be lower in CKD compared with HD and remained statistically different after adjusting for energy intake while the lower intake of phosphorous did not. There were no statistically significant differences in nutrient intake based on sex.

5.3.5 Impact on potassium and phosphorus

Neither CKD or HD demonstrated a consistent difference by quartiles of plant to animal servings and serum potassium or phosphate levels, the number of hyperkalemic or hyperphosphatemic events (**Table 5.3 and 5.4**). Dietary phosphorus and potassium intake was not correlated with serum phosphorus and potassium levels (rho = -0.02, p=0.78 for phosphate and rho =-0.02, p=0.77 for potassium). Plant to animal servings was not correlated with potassium or phosphorus intake or serum potassium or phosphate levels (rho = 0.05, 0.01, -0.11, -0.03 respectively, all p >0.05).

5.3.6 Impact on nutrition and health status

For HD (**Table 5.3**), albumin level was lowest in quartile 3 (moderate plant to animal). Quartile 2 (high animal-moderate plant) had the highest percentage of participants meeting the 1.0 gram per kilogram ideal body weight protein intake target at 61.8%. This was statistically significantly higher than Quartile 4 (high plant-low animal) at 35.3%. The difference in the proportion of participants meeting protein targets failed to reach statistical significance for all other quartile comparisons. Q2 consumed the highest amount of animal protein. The correlation between plant to animal protein servings ratio and protein intake was significant (r=-0.142, p=0.04). Twenty-two HD participants reported very low protein intakes (less than 0.6g/kg), this was not different between plant to animal serving quartiles (Q1=7, Q2=3, Q3=3, Q4=9, p=0.10). There were no differences between quartiles in those who with BMI in the underweight category, Q3 (moderate plant to animal) had a higher percentage of participants in the overweight or obese BMI categories.

For CKD (**Table 5.4**), there were no statistically significant differences in nutrition and health status outcomes. Q2 (High animal-moderate plant) had the highest number achieving

Table 5.3: Potassium, phosphorus and nutrition risk outcomes by plant to animal protein servings quartiles in hemodialysis

Category	Marker	Quartile 1 (n=32)	Quartile 2 (n=34)	Quartile 3 (n=34)	Quartile 4 (n=34)	p-value
Potassium	Potassium (mmol/L)	4.6 ± 0.9	4.6 ± 0.5	4.4 ± 0.4	4.6 ± 0.5	0.41
	% of events considered hyperkalemic per patient	16.9% ± 29.6	11.1% ± 18.0	10.6% ± 16.5	21.0% ± 1.8	0.62
	Had hyperkalemic event, n (%)	15 (46.9%)	16 (47.1%)	18 (52.9%)	17 (51.5%)	0.94
Phosphate	Phosphate (mmol/L)	1.8 ± 0.4	1.7 ± 0.4	1.6 ± 0.4	1.6 ± 0.3	0.42
	% of events considered hyperphosphatemic per patient	41.1% ± 40.9	31.0%± 34.6	26.6%± 23.5	30.0% ± 32.1	0.33
	Had hyperphosphatemic event, n (%)	20 (62.5%)	22 (64.7%)	28 (82.4%)	24 (72.7%)	0.27
	On phosphorus binders, n (%)	26 (81.3%)	26 (76.5%)	23 (65.7%)	23 (67.6%)	0.15
	Mean number of daily phosphorus binders	3.9 ± 2.5	2.8 ± 1.7	2.8 ± 0.9	1.8 ± 0.4†	0.06
Nutrition & health status	Albumin (g/L)	38.3 ± 2.2	36.7 ± 5.1	34.2 ± 4.9†	37.2 ± 4.2	0.01
	Achieving protein recommendation, n (%)	10 (31.3%)	17 (50%)	10 (28.6%)	6 (17.6%)	0.04
	Achieving 30kcal/kg, n (%)	9 (28.1%)	13 (38.2%)	8 (22.9%)	8 (23.5%)	0.47
	Body mass index <18.5, n (%)	0 (0%)	2 (5.9%)	0 (0%)	2 (5.9%)	0.01
	Body mass index 18.5-24.9, n (%)	16 (32.7%)	10 (20.4%)	13 (26.5%)	10 (20.4%)	
	Body mass index 25.0-29.9, n (%)	9 (18.8%)	19 (39.6%)	7 (14.6%)	13 (27.1%)	
	Body mass index >29.0, n (%)	7 (20.6%)	3 (8.8%)	15 (44.1%)	9 (26.5%)	
	Had hospital admission, n (%)	16 (50%)	16 (53.3%)	19 (54.3%)	12 (36.4%)	0.44

% Achieving protein recommendation – protein recommendation based on 1.2g/kg ideal body. Hyperkalemic rate calculated by dividing the number of potassium values above 5.5mmol/L by the total number of potassium values for each participant. Hyperphosphatemic rate calculated by dividing the number of phosphate values above 1.8mmol/L by the total number of phosphate values for each participant. Data displayed as mean ± standard deviation. P-values for continuous variables calculated using 1-way ANOVA. P-values for categorical variables calculated using chi-square. $^{\dagger}P< 0.05$ compared with Quartile 1 of plant to animal servings ratio using 1-way ANOVA with Games-Howell post-hoc test.

Table 5.4: Potassium, phosphorus and nutrition risk outcomes by plant to animal protein servings quartiles in CKD

Category	Marker	Quartile 1 (n=32)	Quartile 2 (n=34)	Quartile 3 (n=34)	Quartile 4 (n=34)	p-value
Potassium	Potassium (mmol/L)	4.7 ± 0.5	4.6 ± 0.5	4.5 ± 0.4	4.6 ± 0.5	0.43
	% of events considered hyperkalemic per patient	7.6% ± 18.9	8.9% ± 16.8	1.8% ± 5.5	6.4% ± 22.8	0.60
	Had hyperkalemic event, n (%)	4 (20.0%)	7 (33.3%)	2 (10.5%)	4 (21.1%)	0.37
Phosphate	Phosphate (mmol/L)	1.4 ± 0.3	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.3	0.81
	% of events considered hyperphosphatemic per patient	9.6% ± 2.6	1.9% ± 5.3	6.8% ± 23.5	15.9% ± 32.7	0.32
	Had hyperphosphatemic event, n (%)	4 (20.0%)	3 (14.3%)	3 (16.7%)	7 (36.8%)	0.32
	On phosphorus binders, n (%)	7 (33.3%)	8 (38.1%)	5 (26.3%)	6 (31.6%)	0.59
	Mean number of daily phosphorus binders	1.8 ± 1.3	2.4 ± 1.3	2.0 ± 0.8	1.8 ± 2.2	0.93
Nutrition risk & health status	Albumin (g/L)	42.1 ± 3.0	40.6 ± 2.9	40.7 ± 3.4	40.7 ± 2.9	0.33
	Achieving protein recommendation, n (%)	17 (81.0%)	17 (85.0%)	14 (73.7%)	15 (78.9%)	0.37
	Achieving 30kcal/kg, n (%)	4 (19.0%)	7 (35.0%)	3 (15.8%)	0 (0.0%)	0.04
	Body mass index <18.5, n (%)	0 (0%)	1 (5.0%)	0 (0%)	0 (0%)	0.49
	Body mass index 18.5-24.9, n (%)	7 (31.8%)	3 (13.6%)	7 (31.8%)	5 (22.7%)	
	Body mass index 25.0-29.9, n (%)	9 (34.6%)	6 (23.1%)	4 (15.4%)	7 (26.9%)	
	Body mass index >29.0, n (%)	5 (23.8%)	10 (50%)	8 (42.1%)	7 (36.8%)	
	Had hospital admission, n (%)	0 (0.0%)	5 (23.8%)	8 (44.4%)	3 (15.8%)	0.01

% Achieving protein recommendation – protein recommendation calculated based on 0.6-0.8g/kg ideal body weight for those with pre-dialysis stage 4-5 chronic kidney disease (CKD). Hyperkalemic rate calculated by dividing the number of potassium values above 5.5mmol/L by the total number of potassium values for each participant. Hyperphosphatemic rate calculated by dividing the number of phosphate values above 1.8mmol/L by the total number of phosphate values for each participant. Data displayed as mean ± standard deviation. P-values for continuous variables calculated using 1-way ANOVA. P-values for categorical variables calculated using chi-square. $^{\dagger}P< 0.05$ compared with Quartile 1 of plant to animal servings ratio using 1-way ANOVA with Games-Howell post-hoc test.

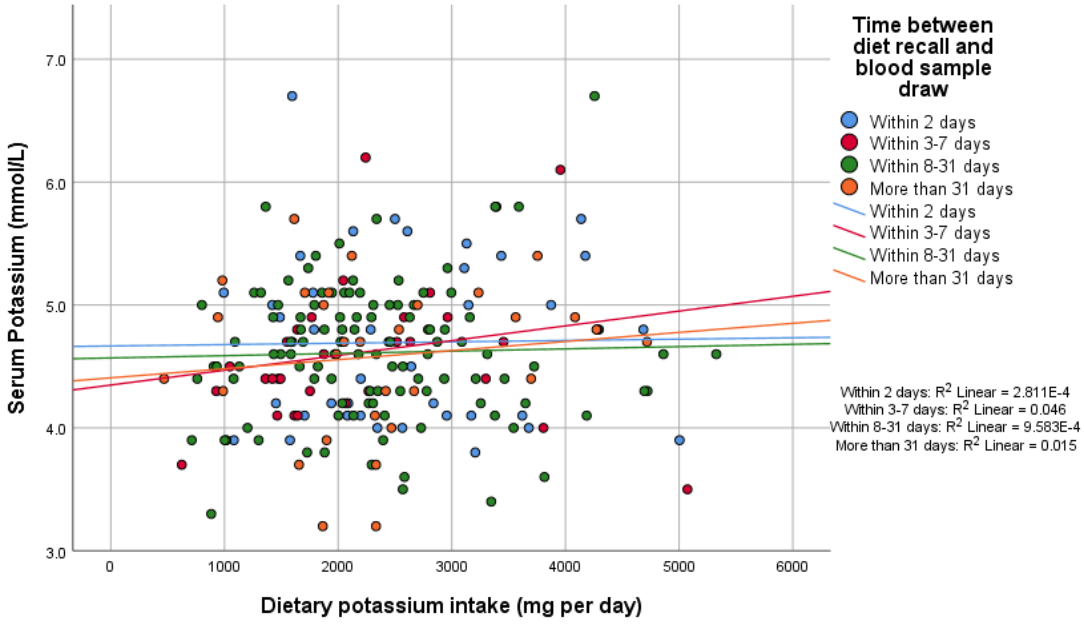
30kcal/kg. The correlation between plant to animal protein servings ratio and energy intake was not significant (r=-0.08, p=0.24). Sixteen participants reported very low protein intake (less than 0.6g/kg), this was not different between plant to animal serving quartiles (Q1=4, Q2=3, Q3=5, Q4=4, p=0.85).

5.3.7 The impact of adjacency between blood draw and diet questionnaire dates

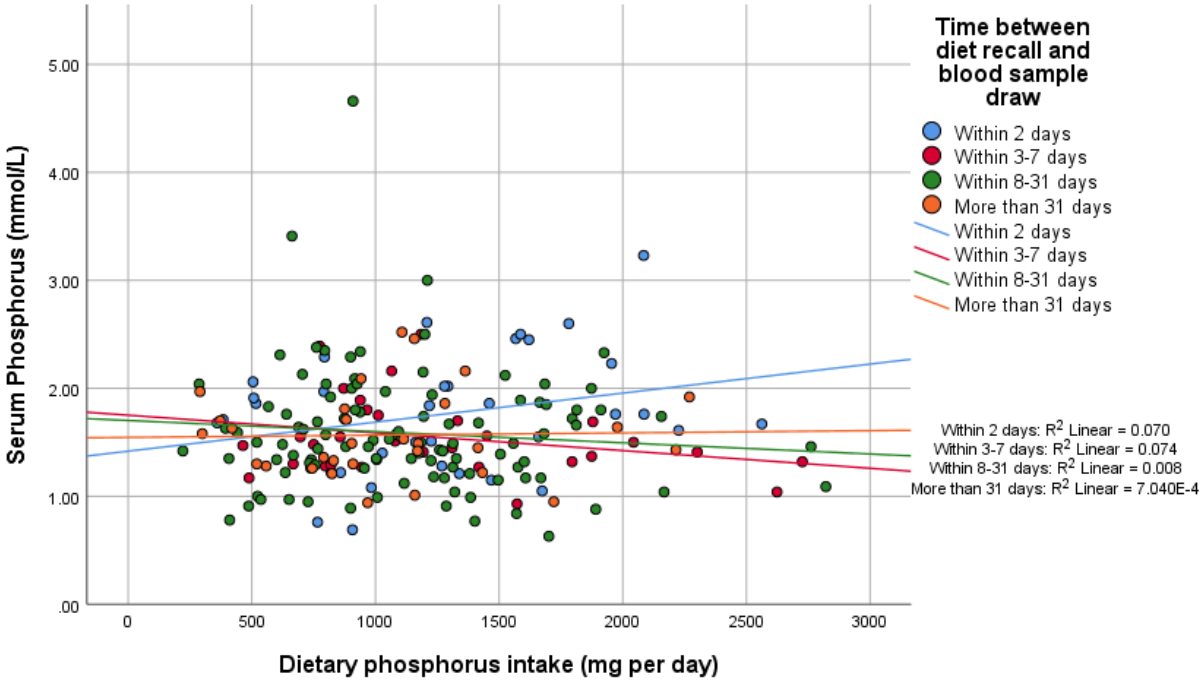
For serum potassium and phosphate, 34.1% and 32.1% of blood samples were drawn within one week of the diet recall and 85.8% and 85.1% within one month, respectively. The Bland Altman plot for mean serum potassium values and the serum potassium values drawn most proximate to the questionnaire suggested that 95.2% (200 of 210) were within -0.98 to 1.10mmol/L. The Bland Altman plot for mean serum phosphate and the proximate phosphate value suggested that 96.5% (195 of 202) were within -0.76 and 0.82mmol/L. With regards to the relationship between serum value dates and dietary intake, for serum potassium all r^2 values were low, at less than 0.05 regardless of proximity (**Figure 5.4A**). This suggests that less than 5% of the variability in the blood samples was explained by the variability in the dietary intake, without an observed affect of proximity. The r^2 values were slightly higher for phosphate than potassium however, they were also low, with all time groups between diet recall and blood sample draw less than 0.074 (**Figure 5.4B**).

Figure 5.4: Dietary intake and serum value scatter plot for potassium (panel A) and phosphorus (panel B) divided by the proximity of the diet recall date and the blood sample date.

A



B



5.4 Discussion

Plant proteins are restricted in low potassium and low phosphorus diets.[29,79] Interest in increasing consumption of plant-based foods and improving diet quality among adults living with CKD is growing.[158-161] There have been a number of publications investigating the benefits of adopting a plant based eating pattern, with reported benefits on metabolic acidosis, hypertension, and the gut microbiome.[158-161] Furthermore, our results help to support the potential for higher plant consumption to be associated with positive diet components such as increased fibre intake and overall diet quality. In this study of adults living with advanced CKD we did not find that the ratio of plant to animal protein source impacted serum potassium or serum phosphate levels. We did not observe higher rates of either hyperphosphatemia or hyperkalemia events amongst those who consume higher proportions of plant to animal protein servings. Those consuming the most plant proteins consumed more fibre and had higher diet quality. Higher fibre intake is associated with lower intestinal potassium absorption [162], reductions in inflammation and lower risk of cardiovascular events.[163] For those on HD, quartile 4 (high plant: animal) took fewer phosphorus binders than quartile 1 (low plant: animal). These are important findings as they contribute to the body of literature that suggests restrictions of plant protein may benefit from re-evaluation.

A potential concern with higher plant protein intake is the impact on nutritional status. In respect to albumin levels, it was noted that while there was a statistically significant difference in albumin across the quartiles among HD participants, whether this is clinically significant needs to be considered. The actual differences between groups was small at 4.1g/L. Additionally, it is possible that the lower albumin levels observed in Q3 may have been more indiciative of health

status rather nutrition status, as this quartile also had the highest rates of hospital admissions and overweight and obesity.

When we explored the proportion within each quartile that was meeting energy and protein requirements, for CKD we found that those who consumed more animal proteins were more likely to meet their energy requirement but not protein targets. This is likely because moderate protein intake is recommended for CKD. For HD, the highest consumers of animal protein, had the highest number of participants achieving protein intake recommendations. This finding agrees with work by Gonzalez-Ortiz et al [112] where a trend of lower protein intake as plant consumption increased was observed. However, as with our study, Gonzalez-Ortiz noted that it was unclear if this was problematic, as those consuming high plant diets had lower Malnutrition Inflammation Scores, indicating better nutritional status.[112] Further studies investigating the impact of high plant diets on nutritional status in HD appear warranted.

With regards to the time differences between the blood sample draw date and the diet recall date, approximately one third of our results were drawn within one week of the questionnaire date and less than one quarter were drawn more than one month apart. We did not observe that blood samples which were drawn closer to the diet recall date were more closely related with estimated intake for either potassium or phosphorus. One potential reason that time differences did not impact serum values could be related to diet variety. A previous study of adults living with CKD reported that diet variety in this population was stable at 5.0-6.7 (out of 10).[61] This is lower than has been reported for the general population at 8.83.[117]

A lack of association between dietary potassium and phosphorus intake and serum values has been previously demonstrated.[152,164] A recently published cross-sectional analyis of CKD and

HD patients from Brazil assessed the correlation between dietary potassium intake and serum potassium values.[164] In this article, no relationship between serum potassium and dietary intake were found for either CKD or HD (r=0.01; p=0.98 and r=-0.06; p=0.46, respectively).[164] Other studies have investigated the impact of increasing plant foods, such as fruits and vegetables [134,135] or plant proteins [42,112], on serum potassium and phosphate levels and their results are in agreement with ours, which suggests that increasing consumption of these foods is not necessarily associated with consuming more potassium or phosphorus overall nor with higher serum levels of eitiher mineral.

One novel aspect of our study was the use of two different diet tools. Consistent with studies in the general population comparing results of the ASA24 and DHQ, we reported that intakes of most nutrients were lower with DHQ [153,155] but in our study these results did not achieve statistical significance. Furthermore, in our small subsample of participants who completed both tools, there were no significant differences. Exploring how the results of these distinct tools in the renal population differ remains an area of further study, though these preliminary results suggest that both methods produce comparable results. Understanding the comparablity between tools is helpful for future studies and post-hoc analyses where pooling of results may be desirable.

With regards to the use of food recalls, a systematic review exploring the impact of potassium on mortality among adults with kidney disease reported that four articles which investigated potassium intake and serum levels among participants with stage 1-3 CKD did not report a clear association between potassium intake and serum potassium levels.[113] All of the studies that were reported in this systematic review used urine estimates for potassium as opposed to dietary recalls.[113] The similarity between those findings and this study helps to

confirm that our findings are not an artifact of the diet recall tools underestimating intake and leading to a type 2 error. Furthermore, both tools that we used have been validated against urine biomarkers [153-155], which suggests that the tools remain resilient to factors such as food prepation or food processing that may impact mineral content of reported foods. An additional strength of using food recall tools as opposed to biomarkers such as 24 hour urine collections, is it allows the opportunity to differentiate between the protein types (plant vs animal). That dietary assessment biomarkers fail to provide granularity in the data to link the measures back to specific foods is a known limitation.[148] More studies that combine the use of different diet assessment tools and biomarkers would likely be beneficial for those conducting research in the renal population.

A strength of this study was our use of serving sizes of whole foods as opposed to specific nutrient weights. There are increasing calls to shift nutrition advice away from single nutrient models in renal nutrition and instead use a more "whole-food" approach.[165] By quantifying intake by serving sizes, this may lead to improved knowledge translation, such that it enables clinicians to discuss whole foods in an easily quantifiable way with patients.

One limitation of the current study was use of self reported data for anthropometrics, hospital admissions, medications and phosphorus binders. For anthropometrics, in this group, participants are likely to be aware of their weight as they are routinely weighed in clinic. For medication use, self reported data likely has some merit, in that medications may appear on a medication list without being taken as prescribed by participants. Additionally, it is unlikely that self reported data would be different between the diet quartiles.

One challenge we encourtered with recruitment was that we did not access language translation services for data collection. Future studies using language services would be beneficial to provide a more comprehensive summary of participant's living with kidney diseases in Alberta as Alberta is compromised of diverse ethnic groups. Additionally, given the large symptom burden of CKD, we had some difficulty recruiting participants as they found the 60 minute time requirement to complete the diet history questionnaire a barrier. Future studies utilizing the most time-effective diet history tools may have an easier time in recruitment.

5.5 Conclusion

In conclusion, in this cohort of adults living with advanced CKD we did not find that those who consumed a higher proportion of plant to animal proteins were more likely to have higher levels of serum potassium or phosphate levels. Though among HD patients, those consuming the most plant proteins and the least animal proteins had the lowest rates of protein intake above 1.0g/kg, though also had higher fibre intake and better diet quailty. Our data supports the re-evaluation of plant protein restrictions especially for the CKD population, and highlights the need for additional studies on high plant protein intake and impacts on nutrition status among HD patients.

Chapter 6: Conclusion

6.1 Executive summary of findings

6.1.1 The current state of medical nutrition therapy for dietary potassium restriction

In Chapter 1, results of our literature and practice reviews related to potassium intake in kidney disease are presented. We hypothesized that low potassium diets would focus mostly on restriction of fruits and vegetables and that this practice would not result in improved clinical outcomes (such as reduced mortality, kidney disease progression or hyperkalemia). Our findings partially supported our hypothesis; results from the literature review suggested that for adults living with kidney disease lower potassium intakes were not associated with faster eGFR decline, mortality or hyperkalemic events. For earlier stages of CKD, evidence suggests that low potassium diets may be harmful, however at later stages of the disease, the evidence was inconclusive. In our practice review, summarizing which foods are restricted and recommended for low potassium diets, we demonstrated that fruits and vegetables and other minimally processed plant based foods are the foods primarily restricted on a low potassium diet. These findings also partially supported our hypothesis about current nutrition therapy practices as we found that current therapy for low potassium diet primarily restricts healthy foods and rarely considers potassium from less healthy, highly processed foods. Our results suggest that the current translation of low potassium diets to specific food recommendations for low potassium diets is not associated with improved patient outcomes and further research into how to optimize diet for serum potassium management is needed.

6.1.2 The prevalence and the impact of potassium additives in foods and the impact of sodium reformulation on potassium additive use in processed foods.

In Chapter 3 the results of the investigation of the USDAs Branded Foods Product Database were presented. We had three hypotheses. First, that potassium additives would be

prevalent in processed foods. Second, that potassium additive use would increase potassium content, and third, that sodium reduced foods would be more likely to contain potassium additives than foods that have not undergone sodium reformulation. Our hypothesis was partially confirmed as we demonstrated that almost 15% of food, across a large variety of food categories contained potassium additives. However, our hypothesis that potassium additives would increase potassium content in foods was not confirmed, as it appeared that some additives, such as acesulfame potassium and potassium sorbate are not associated with increases in potassium content.[66] In contrast, potassium additives that can be used as sodium substitutes, such as potassium chloride and potassium lactate were associated with increases in potassium content. The hypothesis that foods which have undergone sodium reformulation was also partially confirmed in that we reported a higher proportion of sodium free, low sodium and reduced sodium products containing potassium additives compared to products without sodium content claims. However, we also demonstrated that approximately 2.5% of foods which do not make a sodium content claim also contained potassium chloride and lactate which suggests that for those needing to avoid potassium additives, identifying foods by their sodium content claim alone may be insufficient. Our results suggest that while potassium additives are prevalent, it is possible that not all additives contribute significant amounts of potassium to foods. **However, those that are being used for sodium substitutes, such as potassium chloride and lactate, do appear to increase potassium content but can be found in products with and without sodium content claims**.

6.1.3 The current state of medical nutrition therapy for dietary phosphorus restriction

In Chapter 1 results from our literature and practice review as it related to phosphorus restriction are presented. We hypothesized that low phosphorus diets continue to routinely

restrict minimally processed plant foods. Our hypothesis was confirmed as, we demonstrated that, plant proteins remain one of the most commonly restricted food items on low phosphorus diet handouts, with the fewest options suitable alternatives listed. Also related to this objective, we conducted a literature review explicitly exploring how protein type impacts phosphorus intake and serum phosphorus levels. We found that high plant protein intakes were not associated with increased serum phosphorus levels or phosphorus intake, however nutritional status may be better among those who consumed more animal proteins. The results of this review were helpful by demonstrating that a high plant protein was not associated with higher serum phosphorus levels compared to high animal protein diets, however, lower albumin levels were obsereved among the high plant protein diets (and vegetarians) compared to high animal protein diets (and omnivores). However, this finding requires further investigation as it could be hypothesized that current nutrition recommendations for low phosphorus diets may make it more challenging for those who would like to consume more plant proteins to meet adequate protein intake from these foods as there are so few suitable options identified. Our findings suggest that plant proteins remain a primary target of restriction in low phosphorus diets though this practice is not supported in literature and would benefit from review.

6.1.4 The prevalence and the impact of phosphorus additives in the food source

In Chapter 3 we presented the results of our analysis on phosphorus additives in the Branded Foods Product Database. We hypothesized that phosphorus additives would be prevalent in the food source and their use will increase phosphorus content in foods. Our hypothesis was partially supported in that we found approximately 30% of food items contained a phosphorus salt or lecithin. We found these additives across a wide variety of food categories. When individual food categories were considered, non-dairy alternatives, dairy, plant proteins,

and grains contained more phosphorus when the products contained a phosphate salt compared to products without a phosphate salt. However, we were surprised that lecithin specifically appeared to be associated with lower amounts of phosphorus in products compared to products without phosphorus additives, which was not different than products containing phosphorus salts. Our results suggest that while phosphorus additives are prevalent and may increase phosphorus content in some food categories, not all phosphorus additives, specifically lecithin, in all food categories may be associated with increases in phosphorus content, though this remains an area for further study.

6.1.5 How protein source impacts outcomes (serum phosphate levels, hospitalizations, blood work) for adults living with CKD in Alberta (presented in Chapter 5)

In Chapter 5 we presented the results of our cross-sectional analysis of adults living with kidney disease in Alberta. We hypothesized that plant protein foods will not be associated with worse patient and biochemical outcomes and may be associated with improvements in diet quality. Our hypothesis was confirmed as in this cohort there was no correlation between plant protein intake, phosphorus intake or serum phosphorus levels. Furthermore, we demonstrated that those who consumed more plant protein took fewer phosphorus binders, had higher diet quality scores and consumed more fibre that those who were consuming fewer plant proteins. Our results suggest that a diet made up of as many as 4 servings of nuts and seeds, whole grains and legumes may be beneficial for adults living with chronic kidney disease.

6.1.6 Cardiometabolic risk factors, health related quality of life and mental health (presented in Chapter 4); Which diet quality tool may be best suited to describe nutritional adequacy (presented in Chapter 4)

In Chapter 4, we present results of our longitudinal study of adults living with CKD. We hypothesized that adults with CKD who have higher diet quality scores will have better cardio-

metabolic risk factors, health related quality of life and serum potassium and phosphorus levels. Our hypothesis was partially supported in that we demonstrated that those who had higher diet quality had better health related quality of life, fewer depressive symptoms and consumed diets that were more nutritionally adequate. However, there was no relationship between diet quality scores and serum lipids, CRP levels or rates of hyperkalemia. A challenge identified in the interpretation of these results was that the overall diet quality in this cohort was low. Furthermore, diet quality metrics used in the general population may have limited applicability in the CKD population given the unique nutrition needs of this population. Our results suggest that better diet quality is associated with some improvements in patient outcomes, though diet quality in this cohort is low and the applicability of traditional diet quality metrics for CKD is questionable.

6.2 Clinical Implications and Future Directions

This work was initiated by the idea that current medical nutrition therapy for adults living with kidney disease, with regards to potassium and phosphorus restriction, may be misguided. Given the increasing recognition that Canadian's are consuming excess amounts of processed and ultra-processed foods, the work presented in this thesis had a specific goal of examining the impact of food processing on medical nutrition therapy for adults with kidney disease.

For the first time, in Canada, we characterized the amount of processed foods consumed by adults living with kidney disease. Not surprisingly, the majority of energy intake came from processed foods while only ~30% of energy intake was from minimally processed foods. This is a similar pattern to the general Canadian population. That the target of dietary restriction for low potassium and low phosphorus diets so heavily focuses on the smallest portion of the diet is counter-intiutitive. One would anticipate that in order for diet restrictions to be effective they

would need to target foods that people are typically consuming as opposed to foods that people do not routinely consume. We explored this by examining the intakes of those who did and did not have a hyperkalemia event and not surprisingly, reported that those who had hyperkalemia were actually more likely to report higher compliance with low potassium diet recommendations. While the causes of hyperkalemia are multifactorial, it is possible that an unidentified source of potassium in the diet was causing the raise in serum potassium and that neither patients nor clinicians are able to identify these sources as they are not the typical "high potassium foods". Another possibility is the variability of the bioavailability of the potassium in foods. Minimally processed plant foods with intact cell walls appears to have lower bioavailability than animal foods, which appear to have lower bioavaialblity than potassium additives or potassium in processed foods.

To test the idea that typically restricted plant foods, such as nuts, seeds, legumes, soy and whole grains are associated with increased potassium and phosphorus intake and as a result serum levels, we completed a cross-sectional analysis, specifically looking at intake of these foods. We demonstrated that those who consumed more of these foods did not have higher intakes or serum levels, while having higher diet quality, consuming more fiber and using fewer phosphorus binders. This work further highlighted that current medical nutrition therapy does not appear to be well supported. Further exploration is needed to identify which foods may be associated with a rise in serum potassium and/or phosphorus levels, with particular attention not only to the food but also the level of processing.

With regards to potassium and phosphorus content of processed foods, we started this work by exploring additive use and nutrient content of foods listed in the Branded Foods Product Database (BFPD). This database was chosen as the majority of food items in the BFPD are

processed or ultra processed. This enabled us to explore an under-represented portion of the food supply in medical nutrition therapy, despite being the highest proportion of energy intake among this patient population. As anticipated, both potassium and phosphorus additives were found to be highly prevalent and present in a variety foods. What was not anticipated was how infrequently potassium and phosphorus are reported in the database. Additionally, we had not anticipated identifying concerns with accurate nutrient content reporting. When we investigated why improbable amounts of a nutrient may be listed, we discovered that many values are based on food composition tables as opposed to an value derived from an analysis of that specific food. The other cause likely related to the nutrient labeling legislation relevant to both potassium and phosphorus. In most cases phosphorus and potassium would be considered class I or class II nutrients.[166] The legislation stipulates that Class I or II nutritents may be under-reported but not over reported.[166] For adults living with kidney disease who need to limit their potassium and phosphorus intake, this makes understanding how much potassium and phosphorus is in processed foods challenging.

Our understanding of the limitations of nutrient databases to accurately report potassium and phosphorus content of processed foods sheds new light on why current medical nutrition therapy may focus on restriction of minimally processed foods. Minimally processed foods have lab analyzed values for potassium and phosphorus posted in readily accessible databases, such as the USDAs Foundation Foods. This means that clinicans and patients can look up how much potassium and phosphorus is in a minimally processed food quickly and accurately identify if the product is high or low in the nutrient of interest. The same can not be said for processed and ultra-processed foods. Therefore, it may make sense that processed foods do not appear on

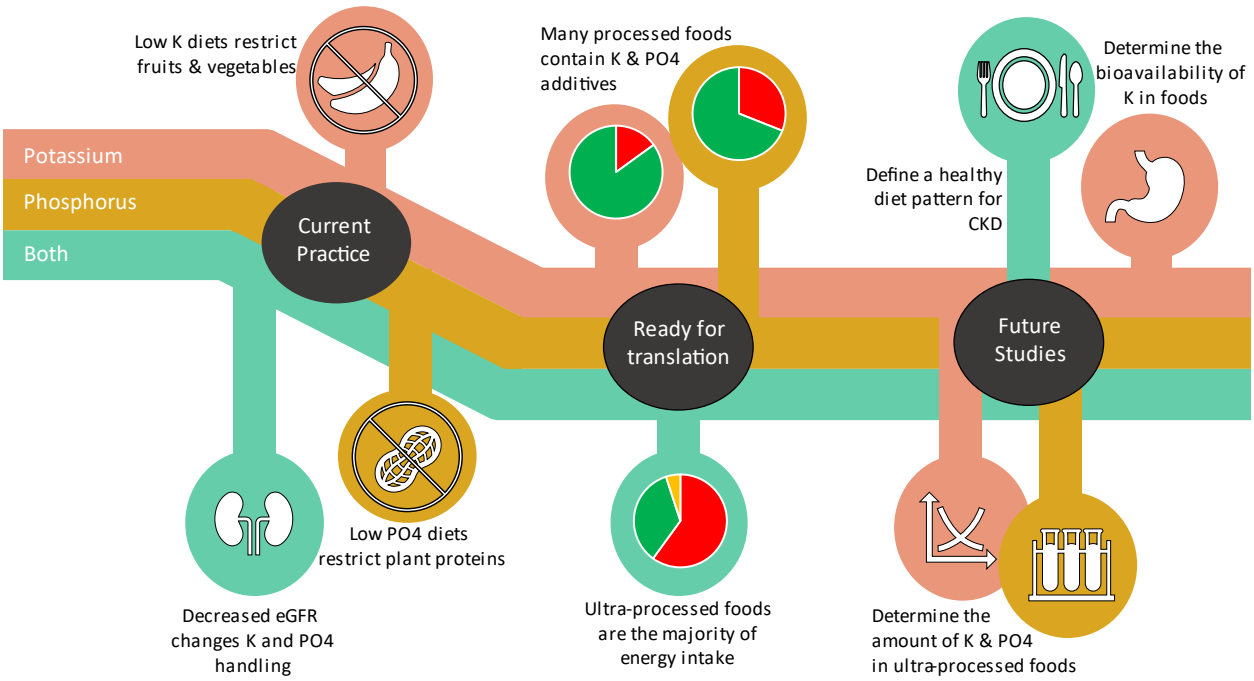
patient handouts because clinicians can not confirm which ones are actually high in potassium and phosphorus.

But – does any of this even matter anyway? Will healthy diets change outcomes for CKD patients? We don't know. In this thesis work we examined diet quality using several different metrics looking for associations with several important outcomes (cardiovascular risk factors, health related quality of life, mental health, nutrient adequacy and serum potassium and phosphorus lab values). Disappointintly, using traditional Mediterranean Diet Scoring metrics we reported that there was no association between Mediterranean diets and cardiovascular outcomes. However, we did observe that those with earlier stages of CKD tended to have higher Mediterranean diet scores, better health related quality of life and mental health scores, however overall the diet quality in our cohort was low. One hypothesis we tested when considering diet quality was exploring the use of standardized scoring cut-offs for Mediterranean Diets, Healthy Eating Index and Healthy Food Diversity and associations with nutritional adequacy in CKD. Very few patients appeared to consume adequate vitamins or minerals to meet the recommended dietary intakes, however there was trend that as diet quality increased so too did nutritional adequacy. One challenge however for traditional diet quality metrics, such as the Healthy Eating Index and Healthy Food Diversity is that higher scores were also associated with higher potassium and phosphorus intake. This limits the applicability of these scores in the advanced CKD population and may explain why those with advanced CKD scored more poorly on these indexes– these diet quality metrics conflict with the kidney diet guidelines. Taken together this highlights two over-arching outstanding questions. How do we define diet quality in CKD population? And would a CKD specific diet quality metric be associated with improved outcomes?

Given the complex and changing nutritional needs of adults living with kidney disease, a healthy diet pattern for the CKD population would need to consider several factors. For example, a healthy diet pattern would need to ensure adequate energy and protein provision to prevent protein-energy wasting, limit excess potassium and phosphorus intake (when indicated) to prevent hyperkalemia and hyperphosphatemia, reduce sodium and fluid intake to maintain euvolemia and ensure micronutrient adequacy. Additionally, further research questions specific to diet quality in CKD are needed to explore: if consuming a low dietary acid load would help promote movement of potassium into the intra-cellular vs extra-cellular space, which dietary changes could help reduce inflammation and whether or not the same diet recommendations are appropriate for both males and females.

In summary, based on the results of this research were have reasonable grounds to hypothesize that current medical nutrition therapy for hyperkalemia and hyperphosphatemia management in kidney disease is incorrect, though there is still much work to be done. Therefore, next steps for this research include completing a potassium bioavailablity feeding study in the kidney disease population to understand how different potassium amounts and sources are absorbed and handled in the body. Further research is needed into potassium and phosphorus food sources and additives bioavailabilty and behavior in the body. And more research is needed on the potassium and phosphorus content of processed foods, with and without these additives. Additional research is needed to define and conceptualize diet quality for the renal population and understand sex differences in CKD and diet quality.

Figure 6.1: Thesis Summary. We demonstrated that current practice focuses primarily on restriction of minimally processed plant foods. New data from this research, ready for translation into clinical practice, is a greater recognition of typical eating patterns among CKD patients (high processed food consumption) and highlighting for patients that many processed foods contain potassium and phosphorus additives. There are many future studies to be done, including more investigations into food and additive potassium and phosphorus bioavailability, and chemical analysis to determine how much potassium and phosphorus is in processed foods. K – potassium, PO4 - phosphorus



6.3 Conclusion

Overall, the research presented in this thesis demonstrated that consumption of processed foods is high among adults living with CKD and that these foods may be a source of potassium and phosphorus additives. Despite this, patient education materials for low potassium and phosphorus diets focus dietary restrictions on minimally processed plant-based foods. Minimally processed plant-based foods are recommended when following healthy dietary patterns such the

Mediterranean Diet. In the general population, Mediterranean Diets are considered beneficial for health. In CKD, higher Mediterranean diet scores were associated with earlier stages of CKD, better health related quality of life and nutritional adequacy but not with cardiometabolic risk factors. However, very few patients in our cohorts achieved high diet quality and therefore firm conclusions cannot be made. Further studies investigating the impact of minimally processed plant-based food consumption on serum potassium and phosphorus, health related quality of life and cardiovascular health appear warranted.

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Appendix 1: Supplementary Material for Chapter 4

Supplementary Table A.1: Macro-and-Micronutrient intake and Diet Quality over five years

Variable	Year 0 (n=50)	Year 1 (n=37)	Year 2 (n=23)	Year 3 (n=19)	Year 4 (n=23)	Year 5 (n=28)	P value
Macronutrients							
Energy (kcal)	1707 (1395-2165)	1662 (1311 - 2110)	1797 (1465 -2070)	1408 (1249 -1619)	1498 (1359 - 1671)	1604 (1250 - 1820)	0.10
Protein (g/d)	77 (66 - 93)	67 (57 - 90)	72 (67 - 92)	70 (60 – 86)	69 (65 – 82)	65 (51 – 81)	0.07
% Energy from Protein	18.6% (14.6 -24.5)	16.3% (15.0 -19.7)	17.3% (14.6 -20.4)	20.4% (14.9 - 23.1	19.5% (17.2 -21.4)	17.3% (15.0 - 21.4)	0.29
Carbohydrate (g/d)	193 (160 - 256)[a]	189 (168 -246)[a]	206 (158 -251)[ab]	160 (122 – 196)[b]	168 (146 – 188)[b]	186 (158 – 220)[ab]	0.03
% Energy from Carbohydrates	43.4% (36.2 - 60.8)	47.8% (44.1 -52.4)	50.1% (42.3 - 53.6)	45.4% (41.0 - 50.1)	44.6% (41.6 - 52.0)	48.1% (41.2 - 56.6)	0.43
Fat (g/d)	63 (46 - 84)[ab]	72 (45 - 93)[a]	76 (47 - 92)[a]	57 (47 – 72)[ab]	57 (50 – 71)[ab]	55 (43 – 68)[b]	0.03
% Energy from Fat	30.4% (21.9 -45.6)	35.0% (31.8 - 40.2)	35.1% (31.8 - 38.8)	36.0% (31.2 - 40.2)	36.7% (31.4 - 39.2)	34.2% (27.2 - 37.5)	0.95
Saturated Fat (SFA) (g/d)	19 (13- 26)	22 (16 - 32)	25 (15 - 36)	19 (17 - 24)	20 (16 – 25)	19 (15 – 24)	0.33

% Energy from SFA	9.2% (6.2 - 15.1)	12.0% (10.1 - 13.3)	11.8% (10.4 - 13.5)	12.0% (9.6 - 15.0	12.4% (9.9 - 13.8)	11.8% (9.5 - 12.5)	0.16
Monounsaturated Fat (MUFA) (g/d)	21.3 (15.9 - 29.4)	24.2 (17.0 -35.1)	27.1 (16.2 -31.9)	21.7 (17.4 -27.1)	22.3 (16.0 - 27.3)	19.8 (14.4 - 27.0)	>0.05
% Energy MUFA	10.5% (7.5 - 17.0)	12.8% (9.1 -17.0)	12.7% (11.1 -14.6)	12.9% (11.2 - 15.8)	10.8% (7.9 - 14.6)	11.8% (8.4 - 14.3)	>0.05
Polyunsaturated Fat (PUFA) (g/d)	11.6 (9.2 -14.8)	12.0 (6.7 - 17.2)	11.9 (8.1 -18.8)	9.2 (8.0 - 12.4)	12.2 (8.9 - 14.4)	9.6 (7.0 - 13.9)	0.17
% Energy PUFA	5.6% (4.3 - 8.1)	6.7% (4.3 - 8.0)	6.4% (5.1 -8.5)	6.2% (5.2 -7.7)	7.0% (5.9 - 7.8)	5.9% (4.5 - 8.0)	0.54
PUFA:SFA	0.6 (0.5 - 0.9)	0.6 (0.4 - 0.7)	0.6 (0.4 - 0.8)	0.5 (0.4 - 0.8)	0.6 (0.5 - 0.7)	0.5 (0.4 - 0.7)	0.54
MUFA:SFA	1.2 (0.9 - 1.4)	1.0 (0.8 - 1.3)	1.1 (0.9 - 1.3)	1.2 (0.9 - 1.4)	1.1 (0.9 - 1.2)	1.1 (0.9 - 1.2)	>0.05
Micronutrients							
Sodium (mg/d)	2301 (1663 - 3221)	2453 (1995 -3399)	2426 (1885 -2826)	2076 (1624 - 2712)	2156 (1605 – 2759)	2446 (1644 – 3076)	0.07
Potassium (mg/d)	2429 (2039-3131)	2491 (2015 - 3049)	2406 (1865 -2703)	2065 (1739 - 2682)	2336 (1987 - 2657)	2330 (1647 - 2952)	0.49
Phosphorus (mg/d)	1105 (947- 1187)	1079 (948 - 1344)	1138 (800 - 1580)	1004 (928 - 1179)	1015 (955 – 1359)	987 (829 - 1203)	0.59
Food Groups (serving per day)							
Vegetables and Fruits	5.4 (3.6 - 6.9)	4.5 (3.3 - 8.0)	3.2 (1.8 - 5.5)	4.7 (2.3 - 5.5)	4.3 (3.1 - 5.8)	4.8 (3.0 - 6.4)	0.08

Grains	5.4 (4.3 - 6.9)	5.4 (3.5 - 6.8)	6.0 (4.3 - 7.7)	4.3 (3.5 - 5.5)	4.6 (4.0 - 6.5)	5.4 (4.1 - 6.7)	0.46
Milk and Alternatives	1.3 (0.6 - 2.1)	1.6 (0.8 - 2.5)	1.6 (0.7 - 2.5)	1.1 (0.6 - 2.3)	1.0 (0.6 - 1.7)	1.3 (0.9 - 2.6)	0.96
Meat and Alternatives	3.0 [a] (2.4 - 3.6)	2.2 [b] (1.8- 3.1)	2.3 [b] (1.8- 3.3)	2.6[a,b] (2.1 - 3.6)	2.9[a] (2.2 - 3.4)	2.0[b] (1.7 - 2.6)	0.02
Diet Quality Measures							
Mediterranean Diet Score (MDS)	4 (3-5)	4 (3-5)	4 (3-5)	3 (3-4)	4 (3-5)	4 (3-6)	0.33
Energy Adjusted MDS	4 (3-5)	4 (3-5)	4 (3-4.8)	4 (3-5)	4 (2.5 – 5)	4 (3-6)	0.80
Davis - Energy Adjusted MDS	3 (2-4)	3 (2-3)	2 (1-3)	2 (1-3)	2 (1.8 - 3.3)	2 (2-3)	0.09
Healthy Eating Index Canada	64.7 (57.1 -71.4)	61.2 (54.0 - 70.1)	55.1 (48.3 - 66.1)	59.2 (51.6 - 65.3)	58.8 (54.4 - 64.9)	63.0 (58.1 - 69.5)	0.39
Adequacy	36.0 (29.3 - 39.5)	33.9 (29.7 -38.3	30.7 (23.9 - 35.8)	29.3 (26.2 - 35.4)	31.0 (27.7 - 36.5)	33.1 (28.6 - 39.4)	0.32
Moderation	24.2 (16.7 - 30.0)	20.0 (18.3 -27.5)	22.5 (15-26.3)	23.3 (19.2 - 27.5)	23.3 (17.9 - 28.3)	25.0 (20.8 - 30.0)	0.40
Variety	6.7 (0.8 - 10.0)	5.0 (0.0 -10.0)	5.0 (0.0 -10.0)	6.7 (0.0 - 8.3)	5.0 (0.0-6.7)	6.7 (3.3 - 10.0)	0.50
Healthy Food Diversity	0.37 (0.31 - 0.48)	0.26 (0.16 - 0.44)	0.27 (0.16 – 0.38)	0.41 (0.27 - 0.46)	0.41 (0.27 - 0.49)	0.32 (0.23 - 0.51)	0.72

Health Value1	0.42 (0.35- 0.52)	0.30 (0.19 - 0.49)	0.32 (0.20-0.43)	0.45 (0.30 - 0.51)	0.45 (0.32 - 0.56)	0.36 (0.26 - 0.58)	0.63
Berry Index	0.88 (0.86 - 0.91)	0.87 (0.85 - 0.90)	0.86 (0.83-0.90)	0.88 (0.86 - 0.90)	0.87 (0.84 - 0.88)	0.87 (0.85 - 0.90)	0.06
Consumption of Minimally Processed and Processed Foods using Nova							
% Energy Nova 1	37.7% (26.9 - 46.9)	30.0% (20.7 - 39.9)	37.4% (27.5 - 48.2)	32.6% (26.4 - 43.1)	35.0% (27.0 - 46.8)	34.6% (22.7 - 42.7)	0.58
% Energy Nova 2	1.7% (0.0 - 4.5)	0.7% (0.0 -3.1)	0.4% (0.0 - 5.2)	0.0% (0.0 - 3.2)	0.7% (0.0-2.6)	0.9% (0.0 - 4.6)	0.43
% Energy Nova 3	4.7% (0.0 - 12.4)	4.6% (1.0 -10.4)	5.9% (0.5 - 19.0)	5.0% (3.1 - 6.9)	6.9% (2.9 - 7.9)	4.1% (0.0 - 12.3)	0.48
% Energy Nova 4	48.6% (41.5 - 63.7)	59.7% (50.8 - 69.0)	45.3% (39.7 - 53.8)	52.1% (40.4 - 64.2)	55.0% (40.7 - 64.4)	56.6% (47.7 - 68.5)	0.32

Data presented as median (IQR); Values with different superscripts are significant at $p<0.05$. Values with different superscripts are significant with $p<0.05$; Davis energy adjusted MDS calculated scoring using proposed benchmarks by Davis et al. [12] Nova (not an acronym) described level of food processing with group 1 unprocessed and minimally processed foods, group 2 processed culinary ingredients, group 3 processed food and group 4 ultra-processed food.

g – grams, d – day, mg – milligrams, SFA – saturated fatty acid, MUFA – monounsaturated fatty acid, PUFA – polyunsaturated fatty acid, MDS – Mediterranean Diet Score