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A Systematic Review of Online Resources on Dietary Management of Hyperphosphatemia in People with Chronic Kidney Disease (CKD)

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ABSTRACT

Background: The Internet search engines and social media websites are prominent and growing sources of dietary information for people with chronic kidney disease (CKD) and their healthcare providers. However, nutrition therapy for CKD is undergoing a paradigm shift, which may lead to inconsistent and conflicting advice online for managing diet-related complications such as hyperphosphatemia.

Purpose of the study: To summarize and evaluate online resources for phosphate-specific diet therapy in people with chronic kidney disease.

Methods: For this systematic review, patient-facing resources on phosphate-specific diet therapy were collected from Google and Yahoo search engines, and the social media website Facebook. Using nine independent search terms, the first 100 hits were reviewed. Dietary advice for food types, food groups, food sub-groups, and individual food items was categorized as “restricted”, “recommended”, “mixed” and “not mentioned”. Additional information on publication date, source, author, phosphorus bioavailability and demineralization were also collected for comparison to dietary advice. Resources that were not intended for people with CKD such as journal publications were excluded from analyses.

Results: After removing duplicates, 199 online resources were available for review from Google and Yahoo, and 33 from Facebook. Dietary advice was primarily focused on restriction of foods high in phosphorus, and processed foods containing phosphorus-based food additives. Although there were notable overlaps in dietary advice, significant inconsistencies were found. Resources ranged from 2005 to 2021 and were primarily from healthcare providers and websites (29% and 39% respectively) and prepared by registered dietitians and medical doctors (65% and 31% respectively). Few resources mentioned phosphorus bioavailability as an important consideration

(16%) or noted demineralization as a phosphorus-lowering strategy (8%). Similar findings were available from Facebook, but limited number of resources limited comparisons.

Conclusion: Results of this study indicate that online resources for phosphate-specific diet therapy are highly restrictive and contain important inconsistencies despite coming from reputable sources. Given the widespread and growing use of online resources by people with CKD, and healthcare professionals to inform dietary choices affecting health outcomes, efforts are urgently needed to establish an evidence-based consensus for phosphate-specific diet therapy. Until then, the findings from this thesis project provide a basis for increasing awareness of the potential for confusion arising from online resources.

Dedicated to

My Parents,

Md Habibur Rahman and **Ayesha Rahman**

For their unconditional support and always believing in me no matter what

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Table of contents

List of Tables

List of Figures

List of abbreviations

ATP	Adenosine triphosphate
ACR	Albumin-to-creatinine ratio
BMD	Bone mineral density
CDC	Centers for Disease Control and Prevention
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CKD-MBD	CKD-mineral and bone disorder
eGFR	Estimated glomerular filtration rate
FGF-23	Fibroblast growth factor-23
GFR	Glomerular filtration rate
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcome Quality Initiatives
PEW	Protein energy wasting
PTH	Parathyroid hormone

Chapter 1

Literature review

1. Overview of chronic kidney disease (CKD)

1.1 Classification of kidney function

The kidneys are critical organs with a variety of functions, including excreting metabolic waste products, and maintaining key homeostatic processes such as fluid, electrolyte and acid-base balance. [1] The kidneys are made up of about a million filtering units called nephrons. The nephrons are the main functional unit of the kidneys, comprised of two principal components: 1) glomerulus and 2) renal tubule. When blood flows into each nephron, it enters the glomerulus where smaller molecules, wastes, and fluid are able to pass into the nephron, and larger components such as blood cells and protein to remain in the blood vessel (filtration). [1], [2]

After filtration, the ultrafiltrate of plasma in the nephron moves along the renal tubules, which continue to modify its composition, producing urine for excretion from the body. During transit through the renal tubules, the majority of useful compounds such as fluid and nutrients are returned to the blood to prevent losses (reabsorption), and some additional compounds are added to the ultrafiltrate for excretion (secretion). [1], [2] The processes of reabsorption and secretion in the renal tubules is tightly regulated, and particularly important for maintaining mineral balance (e.g., phosphorus).

Generally, two important characteristics of kidney function determine kidney disease: 1) filtration rate and 2) filtration barrier. Filtration rate, more specifically glomerular filtration rate (GFR) is a measure of how much blood is filtered by the kidneys. GFR is defined as the volume of plasma that is filtered by the glomeruli per unit of time. [3], [4] In practice, GFR is usually estimated using serum creatinine because creatinine is produced at a fixed rate relative to muscle mass, and almost entirely filtered by the glomeruli with a minimal amount of secretion in the distal nephron. [5] Since GFR is estimated, the term estimated glomerular filtration rate (eGFR) is generally used rather than GFR. [6]

The glomerular filtration barrier is built of multiple layers of highly organized, semipermeable membranes that function to control the filtration process. [7] Albumin is one of the major proteins present in the blood, and since it is a large molecule, it is usually not filtered, and found in very low concentrations in the urine. [8] However, when the filtration barrier becomes impaired, albumin is able to pass through it into urine at abnormally high concentrations (albuminuria). [9] Hence, in addition to eGFR, albuminuria is the other main indicator of kidney disease. [6] Although albuminuria can be assessed using 24-hour urine samples, this is practically challenging. As a result, in practice, albuminuria is generally assessed in relation to creatinine excretion using spot urine sample (albumin-to-creatinine ratio (ACR)), as creatinine is excreted at a nearly constant rate, it can serve as an indicator of time. [10-14]

In general, eGFR $\leq$ 60 mL/min/1.73 m^2, [15] or a urine ACR of 30 mg/g or higher in two of three spot urine specimens indicate kidney disease. [14] In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) classified CKD into six categories (G1, G2, G3a, G3b, G4, and G5) based on eGFR, and three categories (A1, A2 and A3) based on ACR. [11] The combined assessment of GFR categories and ACR level furnishes a more precise evaluation for risk of worsening kidney function and complications. [16-18]

1.2 Global and national burden of CKD

CKD is an emerging and serious health condition, affecting an estimated 843.6 million people worldwide (~13% of population). [19] In 2019, the Global Burden of Disease study estimated about 1.4 million deaths from CKD, which is a 20% increase from 2010 and one of the biggest rises among the top causes of death throughout the world. [20] In the United States, more than 1 in 7 adults (~15%) or 37 million people are estimated to have CKD, and 1 in 3 adults (~80 million) is at risk for developing CKD. [21] CKD is projected to become the 5th most common cause of years of life lost globally by 2040. [22], [23]

The risk of mortality increases with increasing stages of CKD. [24] The leading cause of death in this population is cardiovascular disease (CVD). Increased risk of CVD in the CKD population is largely attributed to disorders of mineral metabolism, chief among them being phosphorus. High serum phosphorus level or hyperphosphatemia is independently associated with increased cardiovascular mortality in CKD patients. [25] Moreover, it is an important clinical feature of chronic kidney disease-mineral and bone disorder (CKD-MBD) which is a common co-morbidity in patients with CKD. [26] A thorough discussion on phosphorus homeostasis process and hyperphosphatemia is essential for the better understanding of the impact of hyperphosphatemia on health outcomes in patients with CKD.

2. Phosphorus homeostasis and hyperphosphatemia in CKD

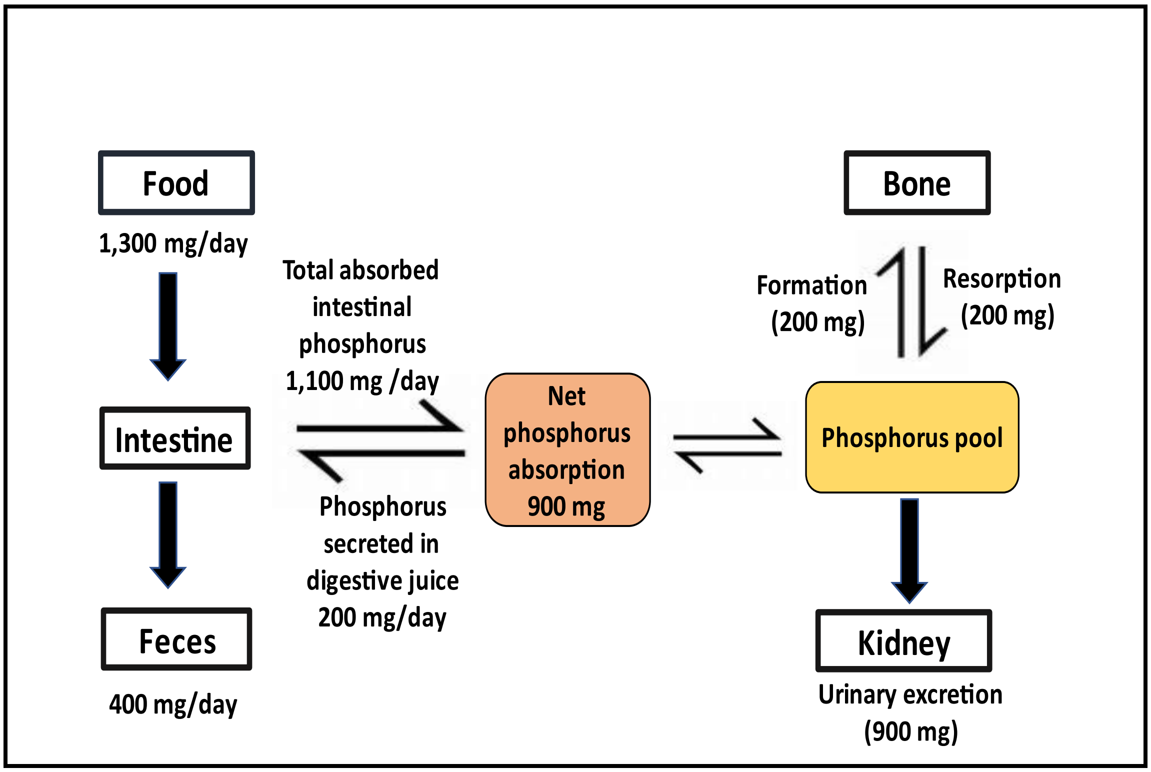
2.1 Phosphorus homeostasis

Following calcium, phosphorus is the second most abundant element in the human body and constitutes approximately 1% of total body weight. [27], [28] The total body phosphorus is approximately 680 g in average healthy adult, the majority of which (80–90%) is present in bone in the form of hydroxyapatite (major component of bone mineral), although the remainder of phosphorus has important roles in numerous body functions. [29-31] Within the body, phosphorus is present as phosphate, which serves as an important donor group (e.g., kinases, ATP), as well as being bound to key macromolecules (e.g., nucleic acids, phospholipids). [32-34]

Phosphorus homeostasis is tightly controlled and involves major regulatory pathways in the intestines, bones, and kidneys. **(Fig-1.1)** A typical Western diet contains approximately two to three times more phosphorus than is required for maintaining body functions (580 mg/d). [35] Assuming a standard intake of 1,300 mg/d of phosphorus from the diet, ~1,100 mg are absorbed in the small intestines, primarily in the jejunum, by both transcellular and paracellular processes where, the former process is mediated by sodium–phosphate (NaPi) type IIb transport protein.

Because ~200 mg of phosphorus is secreted into the digestive tract via pancreatic and intestinal secretions, net phosphorus absorption is about 900 mg (60%); this amount must be excreted by the kidneys to maintain phosphorus balance. Within the body, approximately 200 mg of phosphorus is exchanged daily between the serum phosphorus pool and bone as part of normal bone remodeling process. In determining the concentration of serum phosphorus, the rate of bone remodeling (both resorption and mineralization) is pivotal. [20] In conditions of net bone resorption (demineralization), the additional phosphorus from bone is added to the phosphorus from dietary intake that must be removed by the kidneys. [36]

Figure 1.1. Phosphorus homeostasis in healthy adults.



Note: Values are based on approximate estimates from Shaikh *et al*. (2008). [31]

As noted, the kidneys prevent bioaccumulation of phosphorus by excreting excess phosphorus from the diet and bone in urine. Serum phosphorus is almost entirely filtered at the glomerulus, so the initial tubular fluid concentration of phosphorus is approximately the same as serum phosphorus, and amounts to about 7,200 mg/day, far more than is needed to maintain phosphorus balance. Almost all of the filtered phosphorus is reabsorbed in the proximal renal tubule, and the main regulation of urinary phosphorus excretion occurs in the distal nephron, which is controlled by several factors (e.g., parathyroid hormone (PTH), calcitriol, fibroblast growth factor-23 (FGF-23)). [30]

2.2 Factors regulating phosphorus homeostasis

Phosphorus homeostasis is a complex process, involving several factors and pathways working together to maintain serum phosphorus concentrations within a narrow physiological range (3.5-4.5 mg/dL). [31] In general, phosphorus homoeostasis is regulated by adjusting phosphorus absorption from the intestine, reabsorption from kidney, and mobilization from and/or uptake by the bone. [26] These homeostatic processes are coordinated by the interplay of the PTH and vitamin D (calcitriol) endocrine system that also regulates calcium homeostasis, [31], [37] with several new factors named phosphatonins (notably FGF-23). [38-40] The factors regulating phosphorus homeostasis, and their effects on phosphorus homeostasis are outlined in **Table 1.1.**

The effect of PTH on phosphorus balance is mixed, as it has a primary role in regulating calcium homeostasis. Parathyroid glands have calcium-sensing receptors that monitor the extracellular ionized calcium concentrations and secrete PTH accordingly. [41], [42] When ionized calcium concentration is low, parathyroid gland secretes PTH, which promotes bone resorption, releasing stored calcium and phosphorus. In addition to increasing phosphorus from bone, PTH also stimulates the activity of 1α-hydroxylase in the kidney, which is responsible for synthesizing calcitriol (active vitamin D). [43-45] PTH also acts directly on the kidneys to increase urinary phosphorus excretion by reducing the number of NaPi co-transporters in the renal tubules, reducing phosphorus reabsorption. [46-49]

Calcitriol increases phosphorus retention by enhancing the efficiency of phosphorus absorption in the intestine and reabsorption in the kidney. [50-54] In the intestine, calcitriol upregulates NaPi co-transporters, thereby increasing the absorption of phosphorus [55-57] and in the kidneys, it stimulates NaPi co-transporters to reduce phosphorus excretion or increase phosphorus retention. In addition, calcitriol indirectly promotes phosphorus uptake in bone, in part by inhibiting PTH, thereby reducing bone resorption. [58], [59]

As previously mentioned, other phosphatonins, namely FGF-23, have been found to have important roles in phosphorus homeostasis. Similar to PTH, FGF-23 inhibits renal NaPi co-transporters, leading to increased renal phosphate excretion. [60] However, unlike PTH, FGF-23 reduces calcitriol activity by inhibiting 1α-hydroxylase and stimulating other hydroxylases that inactivate calcitriol and calcidiol (stored vitamin D, its precursor), and mark it for excretion, further increasing urinary phosphorus excretion. [61]

Table 1.1. Factors regulating phosphorus homeostasis and their effects. [41-61]

Factors	Mechanisms of Action	Net Effects
Parathyroid hormone	1. ↓ NaPi co-transporters in renal tubules. 2. ↑ 1α-hydroxylase in the kidney (increases synthesis of calcitriol). 3. ↑ Bone resorption.	↑ Urinary phosphorus excretion.
Calcitriol	1. ↑ NaPi co-transporters in intestine (↑ phosphorus absorption). 2. ↓ 1α-hydroxylase in the renal tubules. 3. ↓ PTH production and secretion.	↓ Urinary phosphorus excretion.
Fibroblast growth factor-23	1. ↓ NaPi co-transporters in renal tubules. 2. ↓ Activity of 1α-hydroxylase reduces the synthesis of calcitriol.	↑ Urinary phosphorus excretion.

NaPi, Sodium-Phosphate

2.3 Hyperphosphatemia in CKD

2.3.1 Definition of hyperphosphatemia

Hyperphosphatemia is defined as an abnormally high serum phosphorus concentration of >4.5 mg/dL. [62], [63] When kidney function decreases, and homoeostatic mechanisms are no longer able to maintain phosphorus balance, hyperphosphatemia develops. [64] Generally, serum phosphorus levels are able to be maintained in the normal range until the advanced stages of CKD (stage 4 and 5). However, the consequences of excess dietary phosphorus in CKD may develop earlier in CKD due to shifts in phosphorus-regulating hormones, known as the trade-off hypothesis. [65], [66] For example, as the PTH levels start to increase in stage 3 CKD to maintain phosphorus balance, bone resorption increases contributing to bone demineralization.

2.3.2 Burden of hyperphosphatemia in CKD

Although hyperphosphatemia is an infrequent condition in the general population, nearly all dialysis-dependent kidney failure patients encounter this condition at some point during the occurrence of their disease. [67] Due to the higher occurrence rate of hyperphosphatemia in the later stages of disease, higher cutoff than normal (5.5 mg/dL) is typically used in kidney failure patients. [68] In patients with kidney failure, the prevalence of this higher hyperphosphatemia cutoff ranges from 50% to 74%. [69] In 2020, 481,050 prevalent cases of hyperphosphatemia in kidney failure patients undergoing dialysis treatment were reported in the United States. [70]

In patients with CKD, a well-known comorbidity is CKD-MBD, of which hyperphosphatemia is an important component. The umbrella term CKD-MBD was established in 2006 by KDIGO and is defined as a systemic disorder of mineral and bone metabolism due to CKD. [71] Vascular calcification, left ventricular hypertrophy and renal osteodystrophy are some of the adverse clinical health outcomes highlighted within the entity termed “CKD-MBD”.

Within the CKD-MBD condition, hyperphosphatemia is thought to be one of the main drivers of vascular calcification. [72], [73] When serum phosphorus levels are elevated, calcium-phosphate salts form deposits in non-bone tissues, leading to calcification. [74], [75] Calcification generally occurs in the blood vessels, heart valves, myocardium, and other soft tissues. [76] Although vascular calcification was initially attributed to calcium-phosphorus supersaturation, in vitro studies suggest that hyperphosphatemia may directly cause phenotypic changes in smooth muscle cells to take part in osteogenesis. Hardening of the arteries in vascular calcification increases vascular resistance, leading to elevated systolic blood pressure, raised pulse pressure, and subsequent left ventricular hypertrophy, which contribute to cardiovascular complications. [77], [78] Owing to the incidence of significant clinical adverse effects of hyperphosphatemia, it is recommended to manage hyperphosphatemia to improve the quality of life and survival rate in patients with CKD. [79], [80]

2.3.3 Strategies to manage hyperphosphatemia in CKD

Hyperphosphatemia is a key priority in the management of patients with CKD, particularly in those with kidney failure undergoing dialysis treatment. [81-83] Three main strategies are used in clinical practice for controlling hyperphosphatemia in CKD patients:

I. Dialysis: Removing phosphorus from the body through ultrafiltration of blood.

II. Drugs: Minimizing intestinal phosphorus absorption using phosphate binders.

III. Diet: Restricting dietary phosphorus intake.

Dialysis is primarily used as a treatment option for the kidney failure patients who have other CKD complications. Dialysis removes waste products, and excess fluids and mineral that are usually removed by the kidneys. [84] However, conventional dialysis treatment can remove only a fraction of excess body phosphorus from the standard diet.

A dietary phosphorus consumption of 1,300 mg/day with a net absorption of 900 mg/day, and a mild demineralization of bone contributing an additional 50 mg/day of phosphorus provides an approximate phosphorus burden of 950 mg/day (6,650 mg/week) (Fig-1.1). Standard maintenance hemodialysis (4 hours, three times per week) removes on average 700-900 mg of phosphorus per session, amounting to a weekly phosphorus removal of only about 2,100-2,700 mg, leaving a large phosphorus excess. [85]

To aid in the management of hyperphosphatemia, use of phosphate binders is common, with more than 95% of patients undergoing dialysis with hyperphosphatemia being prescribed phosphate binders. [81] These drugs work by forming insoluble complexes with dietary and intestinal phosphorus that cannot be absorbed. [82] Despite their efficacy in managing hyperphosphatemia, several issues like high pill burden, and frequent gastrointestinal side effects often lead to poor patient adherence. [83] Besides, use of phosphate binders may incur extra cost for patients, and the healthcare system. [86] Importantly, even when combined with dialysis, phosphate binders cannot remove enough phosphorus to prevent hyperphosphatemia in most patients. [87]

Given the insufficiency of dialysis and drugs, restricting dietary phosphorus is a widely used strategy for managing hyperphosphatemia in CKD. [81] The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition: 2020 Update recommend adjusting dietary phosphorus intake to maintain serum phosphate levels in the normal range. [88] Although there is a general consensus that dietary phosphorus restriction is an appropriate strategy for managing hyperphosphatemia in CKD patients, there is much debate in how this should be accomplished. The following section will describe the dietary sources of phosphorus and dietary management of hyperphosphatemia in patients with CKD, and the associated problems.

3. Dietary management of hyperphosphatemia in CKD

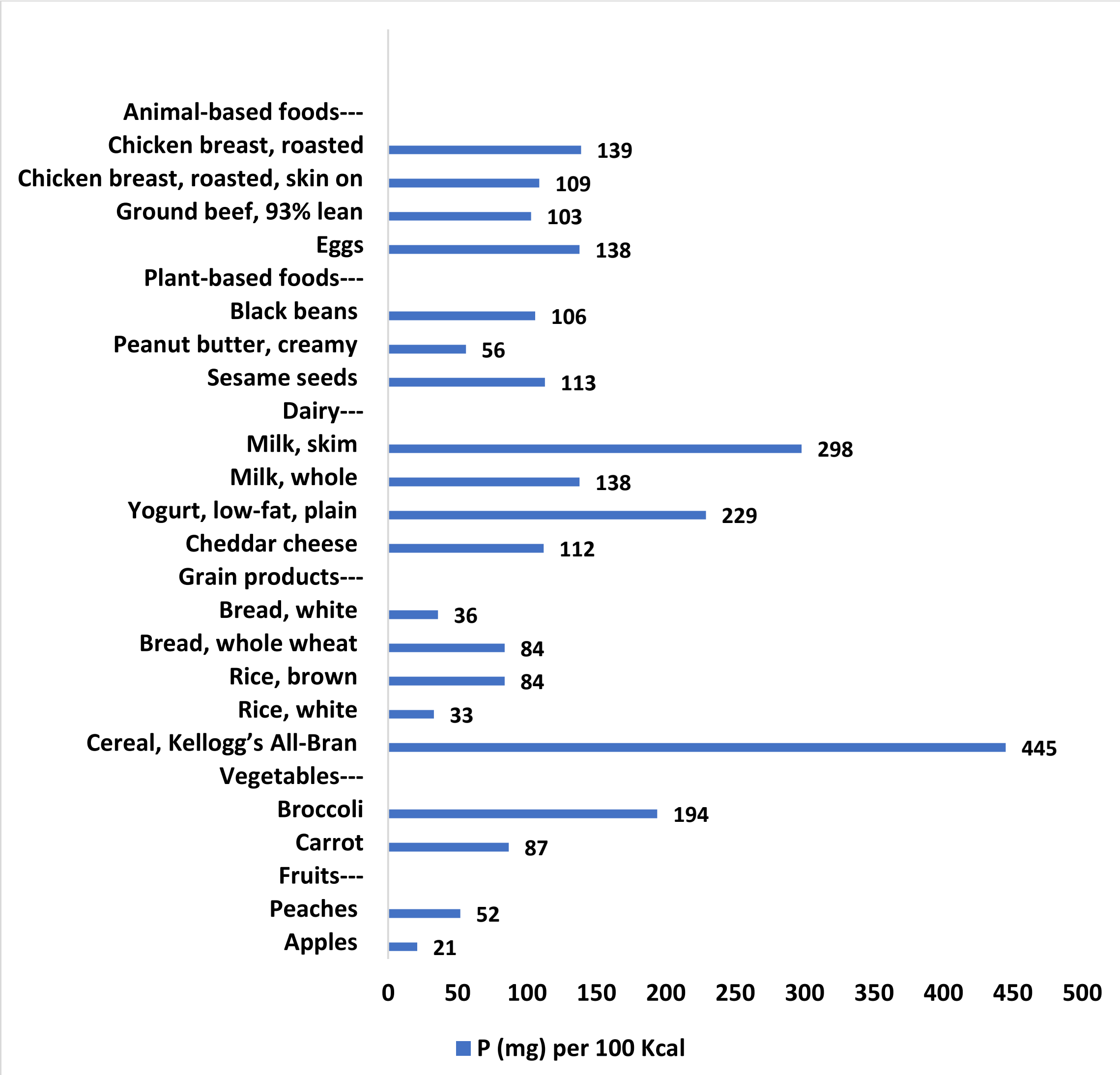
3.1 Dietary sources of phosphorus

Diet is the primary source of phosphorus intake. It then follows that, in patients with CKD, dietary phosphorus is the predominant reason of developing hyperphosphatemia with an important potential to prevent and treat this condition. [89] Since phosphorus exists essentially in all living organisms, it is commonly found in most foods. [90] There are mainly two types of phosphorus present in the diet: 1) Organic phosphorus and 2) Inorganic phosphorus.

1. Organic phosphorus: Organic phosphorus is bound to carbon-containing molecules.[91] This type of phosphorus is present both in animal and plant-based foods but differ considerably in the form. **(Fig-1.2)** [90]

a. Animal-based foods: In a non-vegetarian Western diet, more than one-half of dietary phosphorus comes from animal-based protein foods (meat, poultry, fish, eggs), and dairy products. [91] In these foods, phosphorus is present mainly bound to macronutrients such as protein and lipids. In general, organic phosphorus from animal foods are about 60% bioavailable. [90]

Figure 1.2. Phosphorus content (mg/100 kcal) of animal and plant-based foods in different food groups.



Note: Figure adapted from St-Jules *et al* (2017) [93]

b. Plant-based foods: In plants, phosphorus is mainly present in nuts, seeds, beans, legumes and grains, and fruits and vegetables contain only small amounts of phosphorus. [90] Unlike animal-based phosphorus, phosphorus in plants foods is mostly found in the form of phytic acid or phytate. [91], [92] Generally, plant-based phosphorus is thought to be less bioavailable than animal-based phosphorus (< 40% bioavailability). [94]

2. Inorganic phosphorus: In contrast to organic phosphorus, inorganic phosphorus is found as free phosphate. Although inorganic phosphorus occurs naturally in food, the major source in the diet is from food additives that are used in a wide range of processed foods (**Table 1.2**). [95-97] Phosphorus additives serve a variety of useful functions in processed foods such as increasing shelf life, enhancing color and flavor, emulsifying, and acid-base buffering to name a few. [95], [97] Some common sources of phosphorus-containing food additives include dark colas, enhanced meats, frozen meals, cereals, snack bars, processed or spreadable cheeses, instant food products, and refrigerated bakery products. [89] Generally, inorganic phosphorus has higher bioavailability (70%-80% bioavailability) as compared to organic phosphorus present in natural foods, though the exact bioavailability is controversial. [89], [90] Because phosphorus from food additives has higher bioavailability, the contribution of phosphorus from food additives is disproportionately higher than phosphorus naturally present in foods. [89]

Table 1.2. Commonly used phosphorus additives used in the food industry, their purposes and food sources.

Phosphorus additives	Alternative/chemical names	Purposes	Food sources
Disodium phosphate	Disodium hydrogen phosphate, Sodium phosphate dibasic.	Emulsifier, flavor enhancer and preservative.	Breakfast cereals, condensed milk, cream, evaporated milk, gelatin and processed cheese.
Monosodium phosphate	Monobasic sodium phosphate, Sodium hydrogen phosphate.	Buffering agent and emulsifier	Cola beverages and dry powder beverages.
Phosphoric acid	Orthophosphoric acid or Phosphoric (V) acid.	Buffering agent and flavoring agent.	Cola beverages, carbonated and noncarbonated beverages.
Sodium tripolyphosphate	Sodium tripolyphosphate, Tripolyphosphate.	Buffering agent, texturizer, preservative and flavoring agent.	Meat products, seafood, poultry, vegetable proteins, processed cheese and table syrups.
Tetrasodium pyrophosphate	Sodium pyrophosphate, Tetrasodium phosphate.	Buffering agent, dispersing agent, emulsifier, and color stabilizer.	Processed meats, poultry, seafood, processed cheese and frozen desserts.
Trisodium phosphate	Sodium phosphate tribasic, Trisodium monophosphate.	Emulsifier and preservative	Processed cheese, cheese-based products and breakfast cereals.
Dicalcium phosphate	Dibasic calcium phosphate, Mono hydrogen phosphate.	Calcium and phosphorus supplementation, dough conditioner.	Bakery mixes, cereals, dry powder beverages, flour, food bars, milk-based beverages.

Tricalcium phosphate	Tribasic calcium phosphate, Bone phosphate of lime.	Flavoring agent and anti-caking agent.	Soup mixes, salad dressings, juice powders, processed cheese and yogurt.

Note: Table is adapted from Kalantar-Zadeh *et al* (2010) [89], De Fornasari *et al* (2017) [99] and National Center for Biotechnology Information. [100]

As discussed, different dietary sources of phosphorus have different bioavailability, indicating all dietary sources of phosphorus are not equal in contributing hyperphosphatemia, an issue for dietary management of hyperphosphatemia. Together with a detailed discussion on how bioavailability is an issue, other issues associated with it are discussed in next sub-section.

3.2 Complications associated with dietary management of hyperphosphatemia

As mentioned earlier, the optimal dietary strategy for managing hyperphosphatemia is currently being debated and recent research has provided greater insight into the factors affecting dietary phosphorus exposure. These factors include bioavailability of phosphorus from different dietary sources, and the effects of food processing and preparation (e.g., use of phosphorus additives and demineralization or cooking loss techniques).

First, the bioavailability of phosphorus needs to be taken into consideration, not only the phosphorus contents of food alone. Bioavailability of a nutrient is the fraction of the total amount of nutrient consumed that is digested and absorbed into the body, and available for use. [101] As plant-based protein foods contain phosphorus in the form of phytate, and humans lack the enzyme phytase for digesting phytate, leading to low digestibility. Therefore, even if the total phosphorus content of some plant foods is high, the amount that is absorbed into the body may be relatively low. In contrast, as humans have several enzymes for digesting phosphorus bound to macronutrients (e.g., phosphatases), animal-based foods have higher phosphorus bioavailability. Unlike organic phosphorus, inorganic phosphorus is usually in the form of mineral salt complexes that readily disassociate in water. As a result, inorganic phosphorus is more readily absorbed in the intestinal tract and has the highest bioavailability, limited only by absorption. [89]

Second, food processing and preparation can add or remove phosphorus from foods, dramatically altering the amount of phosphorus in foods away from that which is naturally found. Of these, most attention in the field has been on the addition of phosphorus from food additives, which are widely used and highly bioavailable. Phosphorus additives create problem in two ways-

1) Phosphorus additives are difficult to quantify because phosphorus is not considered a nutrient of public health importance like sodium or saturated fat, and therefore, the amount of phosphorus is not required to be reported on the nutrition facts panel of packaged food. As a result, phosphorus additives are also often unaccounted for in food composition databases. Although phosphorus additives can usually be identified on the ingredients list by the term “Phos-”(Table 1.2), the amount present in foods can vary considerably. In addition, some processed foods do not include ingredient lists (e.g., enhanced meats), and some phosphorus additives are presented with generic names (e.g., modified food starch). [102] Therefore, it is difficult for the patients with CKD to identify phosphorus additives and keep away from it accordingly.

2) The amount of added phosphorus can be substantial, causing low phosphorus foods to become high phosphorus foods. In one study, the phosphorus content of processed foods with phosphorus-containing food additives was three-fold higher than the unprocessed counterparts. [103] Similarly, another study comparing the phosphorus content of similar food items with and without additives showed that both total and soluble phosphorus content were 56% and 64% greater, respectively in the foods containing phosphate additives. [104] This problem seems to be more worrisome in patients with CKD living in low-income communities, as they tend to be more dependent on low-priced processed foods. [105]

In addition to the effects of food processing, certain wet cooking methods such as boiling, and steaming can remove phosphorus from foods by leaching it into the cooking solution in a process called demineralization. [106-111] A number of studies were conducted to investigate the effectiveness of demineralization. Ando *et al* showed that up to 70% phosphorus reduction is possible by cooking beef for 30 minutes. [112] In another study, researchers comparing different cooking methods (boiling in water, steaming, stewing in oil or water, or roasting) found soluble (free) phosphorus reductions were 27% to 43% for fresh and frozen vegetables, 10% to 49% for meat, 7% for pasta, and 23% for rice on a dry weight basis. [113] Although demineralization can remove large amounts of phosphorus, it has several potential limitations and drawbacks as a phosphorus-lowering strategy. Demineralization can be time consuming, and may not be applicable for, or can reduce the palatability of many high-phosphorus foods (e.g., dairy products. and peanut butter). In addition, other water-soluble nutrients that may be beneficial for patients (e.g., iron) can also be eliminated by these processes. [94], [114] The problems discussed above are important sources of inconsistencies observed in the dietary guidance for lowering phosphorus intake in patients with CKD. The traditional low phosphorus diet did not take into consideration these issues, which is the principal reason for the arising discrepancies in the dietary advice for CKD patients. An overview of low phosphorus dietary advice for patients with CKD and associated controversies are presented in **Table 1.3.**

Table 1.3. Summary of low phosphorus dietary strategies for patients with CKD and associated controversies.[8], [79], [80]

Strategy	Rationale	Considerations and Controversies
Avoid processed foods with phosphorus additives	1. Contains additional phosphorus. 2. Bioavailability is approximately 70%-80%.	1. Difficult to detect and avoid. 2. Low phosphorus foods become high phosphorus foods.
Avoid whole grains	Refining grains removes most of the phosphorus.	1. Whole grains contain plant-based phosphorus which is <40% bioavailable. 2. Whole grains are important source of nutrients (e.g., fiber, magnesium).
Avoid animal-based protein foods	Animal-based protein foods are rich sources of phosphorus.	1. Animal proteins are an important source of nutrients (e.g., protein, omega-3 fatty acids, iron, zinc).
Avoid dairy products	Dairy products are rich sources of phosphorus.	1. Dairy products are important sources of nutrients (e.g., protein, calcium, vitamin D).

Avoid plant-based protein foods	Plant-based protein foods are rich sources of phosphorus.	1. Plant phosphorus is <40% bioavailable. 2. Plant-based protein foods are an important source of nutrients (e.g., fiber, magnesium).
Follow Demineralization	Demineralization or cooking loss may help reducing phosphorus.	1. Demineralization may remove other important nutrients along with phosphorus. 2. Not applicable for all foods (e.g., dairy products, peanut butter). 3. May causes the foods to become less palatable and less attractive. 4. Requires meals prepared from scratch, which takes time, skills and resources that may not be available.

The presence of inconsistent and conflicting dietary advice for managing hyperphosphatemia in CKD patients has been identified in patient handouts from Canadian healthcare organizations. [115] However, online search engines and social media websites are a easily accessible source of healthcare information for many CKD patients. These online sources share information on phosphorus-specific diet therapy for CKD patients. The role of various search engines and social media websites in the field of CKD healthcare, specifically on disease management and their potential disadvantages are discussed in the next section.

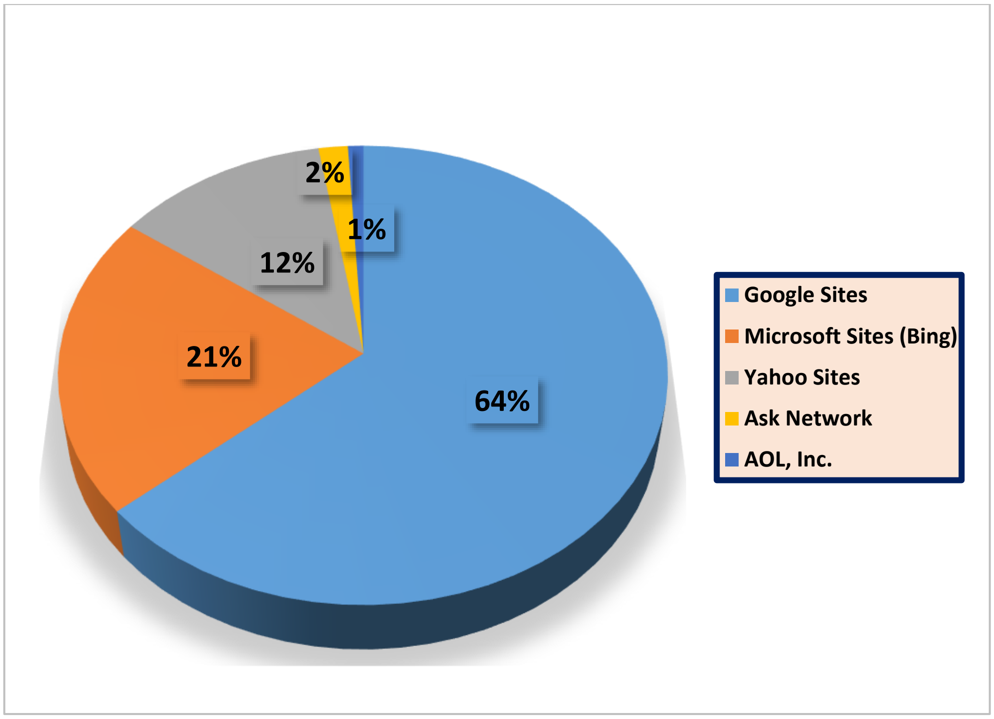
4. Role of online resources in dietary management of hyperphosphatemia

4.1 Utilization of the online resources

The 21st century has been called the era of Internet, and aligned with that, the Internet has become one of the most important means of securing health and medical information for people all over the world. [116] Approximately 80% of Americans use Internet search engines to explore online resources that contain information about their disease, treatment strategies, and alternatives on their own. [117] Along with this, Internet-based websites are an important source of information for the disease management of people with CKD. [118] Several research studies have shown that Internet use among people with CKD has increased significantly in the past decade, [118-120] and many people with CKD rely on the online websites for information related to care [118], including up to 58% of people with kidney failure undergoing dialysis treatment. [121] In addition to patients, the Internet has become an important resource for health care professionals to inform treatment decisions. [116]

Google, Yahoo!, Bing, Baidu and Ask.com are some of the popular and effective search engines worldwide in assisting health professionals, and lay users to get health and medical information. [116] According to comScore 2013, Google, Yahoo and Bing are the top-tier search engines because they have been the preeminent three search providers in the United States, possessing over 95% of search traffic. [122] Market shares of the Internet search engines is the primary indicator of popularity and use. **(Fig-1.3)**

Figure 1.3. Pie chart of search engine market share (2016). [122]



Google accounts for about two-thirds of the Internet searches in the United States, and this amount appears to be growing. [116], [123] Google is highly rated on ease of use, coverage, speed, and reliability. Research studies indicated that over 80% of first visits come from web search and of these visits, more than 76% are for Google's Search Worldwide because of its advantages. [124], [125] Another important feature of Google is that it provides country-based versions of its website, which enables region-specific searching for healthcare purposes. [126]

Consistent with these advantages and popularity, it is evident from several research studies that Google is the top priority search engine in collecting healthcare information by the patients with CKD. [118], [126] To identify the internet search trends data as a unique resource for monitoring online health information-seeking behavior, one recent study investigated the global public interests on CKD information using Google. [126] In a cross-sectional study investigating the patterns of Internet use by parents of children with CKD, Google websites were the first choice for collecting information regarding their disease. [127] Besides, studies focusing on the evaluation of contents and quality of the CKD healthcare information in websites, researchers chose Google websites as the first priority search engine. [118]

Undoubtedly, Google is the most popular search engine over others, but there are few others that are popular as well. Yahoo is a well-known search engine and was ranked 2nd based on market share before Bing entered the search engine market. Yahoo is one of the pioneering search engines, and is still popular for its quick results and high coverage. However, since Yahoo was launched prior to Bing, many online users are more familiar and accustomed to use Yahoo search engine for information, despite it being ranked below Bing. [125] Like Google, Yahoo is another preferred search engine in the online-based research on patients with CKD. [118], [128]

Together with internet-based search engines, social media websites equally become a well-known stockpile of health information, including for people with CKD. [129] Since the advent of social media in 2004, a rising percentage of patients all over the world use this technology for health-related purposes. Social media offers a platform where people can easily access medical information from sources ranging from healthcare professionals to laypersons conveying personal experiences of health and illness. [130] As many people spend significant number of hours on social media, the healthcare field has embraced it and includes it into several current health care strategies. [130] In fact, over 80% of State health departments in the United States contain social media accounts in the purpose of helping patients through social media. [131]

The use of social media by patients with CKD for disease management information and peer support is increasing. [132] People with CKD are often motivated towards self-management and note the value of other patient's personal opinions and experiences on their health. [132] In these cases, social media websites are often the first choice for CKD patients actively using social media websites. Indeed, research suggests that approximately 75% of health decisions made by patients were influenced from the information they collected through their own research from social media websites. [133]

Of different social media websites, Facebook is the most popular, highly accepted and more reliably used social media networking site throughout the world. A revolution appeared in Facebook usage after 2010 when Facebook users exceeded one billion people worldwide, a number that reflects one-eighth of the world's population. It is the most popular social media website in the United States where approximately seven-in-ten adults (~69%) reported their use of Facebook for healthcare purposes. [134], [135]

Several studies have used Facebook in research involving CKD populations. [136], [137] In one study, Facebook was used to recruit kidney transplant recipients, and was found to be a cheaper option compared to traditional methods. [136] In other studies, people with CKD have reported that their information needs were better met through Facebook than through healthcare professionals own social media platforms. [137], [138] Of interest, diet was one of the major kinds of information that people with CKD reported seeking through Facebook. [139] Facebook has also been found to be an effective medium for educating people with CKD. [134], [140] However, like many other technology-based tools, online resources available in the Internet search engines and social media websites have numerous disadvantages (**Table 1.4)**.

4.2 Disadvantages of the online resources

Although Internet search engines have been widely promoted as potential sources of educational resources for patients with CKD, several studies have found that the quality of online information is often less than ideal. For instance, websites rarely provide the sources or strength of evidence. As an example, the National Kidney Disease Education Program (NKDEP) websites are well-recognized public websites that offer reliable information for people with CKD and healthcare providers. However, in one online resource-based study exploring the quality of online resources, websites of NKDEP were not included in the top-ranked websites based on DISCERN scores due to the lack of clear source of information presented, dates of the source of information, and discussions about areas of uncertainty. [128] Because websites are rarely updated, online information may not be based on the most current evidence and can become outdated in rapidly evolving fields. These issues can lead to severe inconsistencies and contradictions in the information provided for CKD patients, particularly as many websites obtain information from older websites. [141], [142] Misinformation can have serious consequences like worsening of disease condition or even death, especially in younger and newer patients who are less familiar with CKD. [140] [143]

Another issue associated with Internet websites is that the information provided may not align with the information needs identified by people with CKD, resulting in knowledge gaps in self-management. It was estimated that less than 30% of the content that patients identified as important for CKD self-management, including dietary information, were available in online sources. [117] For example, it was found that many websites did not offer sufficient information or referred to other sources to instruct patients on how to cope with life on dialysis. These findings indicate that many of the current CKD websites offer insufficient utility or benefit to serve as effective educational resources for people with CKD. [117]

Social media may actually be a greater source of misinformation online. [134], [138], [139] The authors sharing medical information on social media sites are often unknown, unreferenced, or identified by insufficient information. In addition, while evidence-based medicine discourages anecdotal reports, social media resources tend to encourage them based on individual patient experiences for overall medical knowledge in specific health concern. As anyone with access to social media can share healthcare advice or recommend treatments for dealing with health conditions, there is an obvious potential to spread wrong and self-believed ideas in social media resources. [144] For example, unverified health advice shared on Twitter misguided Nigerians to drink excessive amounts of salt water to fight against Ebola, which resulted in 12 hospitalizations and two deaths. [144], [145] Though similar consequences of dietary misinformation for people with CKD have not been linked traced to social media, the example of Ebola anecdote indicates that social media could be an important source of distributing misinformation on CKD as well.

The inconsistency of information shared via the resources in social media networks poses another significant challenge. People with CKD using social media websites reported facing inconsistent information despite an expectation for unambiguous information and guidance from the resources shared by healthcare professionals. [138] The consequences of inaccurate and inconsistent information on social media are exacerbated by the fact that information can be distributed rapidly and broadly compared to other online platforms. [145]

Table 1.4. Disadvantages of online resources with examples and potential impact. [128-145]

Disadvantages of online resources	Example	Potential impact
Low quality information	1. Unspecified source, author and date for published information. 2. Healthcare information not based on most current evidence. 3. Wrong and misleading healthcare information without any evidence.	1. Misinformation, confusion and skepticism about health advice in general. 2. Produce inconsistent and conflicting information. 3. Leads to worsening of disease condition or death.
Content gaps	Webpages containing insufficient healthcare information.	Fails to meet patient's information needs.
Limited accessibility	Limited access for information for patients.	Poor reliability and dissatisfaction.
Spreading of information	Spreading of inaccurate information.	Confusion among mass people.

5. Prior research and the knowledge gap

Since online resources are a major growing source of health information for patients with CKD and the healthcare professionals; it warrants study. Prior research has focused on the content and quality of online resources, and their potential use to promote kidney disease education (discussed in Section 4). However, research on dietary advice for phosphate-specific diet therapy is very limited.

A recent study evaluated patient handouts from Canadian healthcare and renal program websites focusing low phosphorus diets in CKD patients. The preliminary findings from this study suggested that inconsistencies are a major problem. [115] These inconsistencies appear to be impacting clinical practice. A cross-sectional survey of 187 renal dietitians found that dietary advice on phosphorus-based food restriction was inconsistent, and many dietitians reported low confidence in explaining what makes a low phosphorus diet. [146]

Undeniably, the inconsistent and conflicting dietary information for managing hyperphosphatemia is detrimental for the patients with CKD. Simultaneously, it raises doubt on the expertise of the caregivers and the quality and reliability of the healthcare providers. All of these serious issues urge the necessity of conducting research on it.

6. Purpose of this research

The purpose of this research is to summarize and evaluate the available online resources on dietary management of hyperphosphatemia to generate novel data on the extent of inconsistencies present in the dietary advice for people with CKD.

References

1. Firth J, John D., Steve H and Robert U, 'Structure and function of the kidney', in John Firth, Christopher Conlon, and Timothy Cox (eds), Oxford Textbook of Medicine, 6 edn (Oxford, 2020; online edn, Oxford Academic, 1 Jan. 2020).
2. Pollak MR, Quaggin SE, Hoenig MP, Dworkin LD. The glomerulus: the sphere of influence. *Clin J Am Soc Nephrol.* 2014;9(8):1461-1469.
3. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatr Nephrol*. 2007;22(11):1839-1848.
4. Sujoy G, Andrew C. Section 5 - Chronic complications, (Second Edition), Churchill Livingstone, 2012, Pages 165-226.
5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999;130(6):461–470.
6. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA*. 2015;313(8):837-846.
7. Arif E, Nihalani D. Glomerular Filtration Barrier Assembly: An insight. *Postdoc J.* 2013;1(4):33-45.
8. "KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease". *Kidney Int Suppl*. 3 (1): 1–150.
9. Lamb E.J. MacKenzie F. Stevens P.E. How should proteinuria be detected and measured? *Ann Clin Biochem.* 2009; 46: 205-217.

10. McTaggart MP, Price CP, Pinnock RG, Stevens PE, Newall RG, Lamb EJ. The diagnostic accuracy of a urine albumin-creatinine ratio point-of-care test for detection of albuminuria in primary care. *Am J Kidney Dis*. 2012;60(5):787-794.
11. Kidney Disease: Improving Global Outcomes (KDIGO) 2012: Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 3: 1–150, 2013.
12. National Clinical Guideline Centre: Chronic Kidney Disease (Partial Update): Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care, London, UK, National Institute for Health and Care Excellence, 2014.
13. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med*. 2006;23(8):2473-2483.
14. Nah EH, Cho S, Kim S, Cho HI. Comparison of Urine Albumin-to-Creatinine Ratio (ACR) Between ACR Strip Test and Quantitative Test in Prediabetes and Diabetes. *Ann Lab Med.* 2017;37(1):28-33.
15. Ameh OI, Ekrikpo U, Bello A, Okpechi I. Current Management Strategies of Chronic Kidney Disease in Resource-Limited Countries. *Int J Nephrol Renovasc Dis*. 2020; 13:239-251.
16. Levin A, Stevens PE. Summary of KDIGO 2012 CKD guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int.* 2014; 85:49–61.

17. Levey AS, Tangri N, Stevens LA. Classification of chronic kidney disease: a step forward. *Ann Intern Med.* 2011; 154:65–7.

18. Tonelli M, Muntner P, Lloyd A, *et al*. Using proteinuria and estimated glomerular filtration rate to classify risk in patients with chronic kidney disease: a cohort study. *Ann Intern Med*. 2011; 154:12–21.

19. Shrestha N, Gautam S, Mishra SR, Virani SS, Dhungana RR. Burden of chronic kidney disease in the general population and high-risk groups in South Asia: A systematic review and meta-analysis. *PLoS One*. 2021;16(10): e0258494.

20. Jager K.J. Kovesdy C. Langham R. *et al*. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Kidney Int.* 2019; 96: 1048-1050.

21. https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html. Accessed date July 2022.

22. Li PK, Garcia-Garcia G, Lui SF, Andreoli S, Fung WW, Hradsky A, *et al*. Kidney health for everyone everywhere-from prevention to detection and equitable access to care. *J Ren Care.* 2020; 46(1):4–12.

23. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, *et al*. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet.* 2018;392(10159):2052–2090.

24. Liu P, Quinn RR, Lam NN, *et al*. Progression and Regression of Chronic Kidney Disease by Age Among Adults in a Population-Based Cohort in Alberta, Canada. *JAMA* Net w Open. 2021;4(6): e2112828.

25. Zhou C, Shi Z, Ouyang N, Ruan X. Hyperphosphatemia and Cardiovascular Disease. *Front Cell Dev Biol.*2021; 9:644363.

26. Shaman AM, Kowalski SR. Hyperphosphatemia Management in Patients with Chronic Kidney Disease. *Saudi Pharm J*. 2016; 24(4):494-505.

27. Bellasi, A., Kooienga, L., Block, G.A., 2006. Phosphate binders: new products and challenges. *Hemodial. Int*. 10, 225–234.

28. Farrow EG, White KE. Recent advances in renal phosphate handling. *Nat Rev Nephrol*. 2010; 6:207–217.

29. Manghat P, Sodi R, Swaminathan R. Phosphate homeostasis and disorders. *Ann Clin Biochem*. 2014; 51(Pt 6):631-656.

30. Fleisch H, Bonjour JP, Troehler U. Homeostasis of inorganic phosphate: an introductory review. *Calcif Tissue Res*. 1976;21 Suppl:327-331.

31. Shaikh A, Berndt T, Kumar R. Regulation of phosphate homeostasis by the phosphatonins and other novel mediators. *Pediatr Nephrol*, 2008; 23:1203-1210.

32. Cohen P. The structure and regulation of protein phosphatases. *Annu Rev Biochem*. 1989; 58:453-508.

33. Hubbard SR and Till JH. Protein tyrosine kinase structure and function. *Annu Rev Biochem* ,2000; 69: 373–398.

34. Hunter T and Cooper JA. Protein-tyrosine kinases. *Annu Rev Biochem*, 1985; 54: 897–930.

35. Vorland CJ, Stremke ER, Moorthi RN, Hill Gallant KM. Effects of Excessive Dietary Phosphorus Intake on Bone Health. *Curr Osteoporos Rep*. 2017 Oct;15(5):473-482.

36. Steele TH. Effect of phosphorus depletion on the renal transport of phosphate. *Adv Exp Med Biol*, 1978; 103: 343–355.

37. Berndt T, Kumar R. Phosphatonins and the regulation of phosphate homeostasis. *Annu Rev Physiol*, 2007;69:341–359.

38. Kumar R. Phosphatonin—a new phosphaturetic hormone? (Lessons from tumour-induced osteomalacia and X-linked hypophosphataemia). *Nephrol Dial Transplant*, 1997;12: 11–13.

39. Kumar R. Tumor-induced osteomalacia and the regulation of phosphate homeostasis. *Bone* 27: 333–338, 2000.

40. Schiavi SC and Moe OW. Phosphatonins: a new class of phosphate regulating proteins. *Curr Opin Nephrol Hypertens,* 2000; 11: 423–430.

41. Garrett, J.E., Capuano, I.V., Hammerland, L.G., Hung, B.C., Brown, E.M., Hebert, S.C., Nemeth, E.F., Fuller, F. Molecular cloning and functional expression of human parathyroid calcium receptor cDNAs. *J. Biol. Chem*. 1995; 270, 12919–12925.

42. Riccardi, D., Park, J., Lee, W.S., Gamba, G., Brown, E.M., Hebert, S.C. Cloning and functional expression of a rat kidney extracellular calcium/polyvalent cation-sensing receptor. *Proc. Natl. Acad. Sci USA* 1995; 92, 131–135.

43. Boyle IT, Gray RW, and DeLuca HF. Regulation by calcium of in vivo synthesis of 1,25-dihydroxycholecalciferol and 21,25-dihydroxycholecalciferol. *Proc Natl Acad Sci USA*, 1971; 68: 2131–2134.

44. DeLuca HF. The kidney as an endocrine organ for the production of 1,25-dihydroxyvitamin D3, a calcium-mobilizing hormone. *N Engl J Med*, 1973; 289: 359–365.

45. Garabedian M, Holick MF, Deluca HF, and Boyle IT. Control of 25-hydroxycholecalciferol metabolism by parathyroid glands. *Proc Natl Acad Sci USA*, 1972; 69: 1673–1676.

46. Spanos, E., Freake, H., Macauley, S.J., Macintyre, I. Regulation of vitamin D metabolism by calcium and phosphate ions in isolated renal tubules. *Biochem. J.* 1981; 196, 187–193.

47. Patwardhan, V.N., Nhavi, N.G. The absorption of phosphates from the intestine. *Biochem. J.* 1939; 33, 663–670.

48. McGowan, J.P. Some considerations regarding and investigations into calcium and phosphorus metabolism. *Biochem. J.* 1933; 27, 934–942.

49. Sutcliffe, H.S., Martin, T.J., Eisman, J.A., Pilczyk, R. Binding of parathyroid hormone to bovine kidney-cortex plasma membranes. *Biochem. J.* 1973; 134, 913–921.

50. Tanaka Y and DeLuca HF. The control of 25-hydroxyvitamin D metabolism by inorganic phosphorus. *Arch Biochem Biophys*, 1973; 154: 566– 574.

51. Tanaka Y and DeLuca HF. Role of 1,25-dihydroxyvitamin D3 in maintaining serum phosphorus and curing rickets. *Proc Natl Acad Sci USA*, 1974; 71: 1040–1044.

52. Tanaka Y, Frank H, and DeLuca HF. Biological activity of 1,25-dihydroxy vitamin D3 in the rat. *Endocrinology*, 1973; 92: 417–422.

53. Tanaka Y, Frank H, and DeLuca HF. Intestinal calcium transport: stimulation by low phosphorus diets. *Science*, 1973; 181: 564–566.

54. Tanaka Y, Frank H, and DeLuca HF. Role of 1,25-dihydroxycholecalciferol in calcification of bone and maintenance of serum calcium concentration in the rat. *J Nutr;* 1972; 102: 1569–1577.

55. Katai, K., Miyamoto, K., Kishida, S., Segawa, H., Nii, T., Tanaka,mH., Tani, Y., Arai, H., Tatsumi, S., Morita, K., Taketani, Y., Takeda, E. Regulation of intestinal Na+-dependent phosphate co-transporters by a low-phosphate diet and 1,25-dihydroxy vitamin D3. *Biochem. J.* 1999; 343 (Pt 3), 705–712.

56. Danisi, G., Bonjour, J.P., Straub, R.W. Regulation of Na dependent phosphate influx across the mucosal border of duodenum by 1,25-dihydroxycholecalciferol. *Pflugers Arch*. 1980; 388, 227–232.

57. Danisi, G., Caverzasio, J., Trechsel, U., Bonjour, J.P., Straub, R.W. Phosphate transport adaptation in rat jejunum and plasma level of 1,25-dihydroxyvitamin D3. *Scand. J. Gastroenterol*, 1990; 25, 210–215.

58. Friedlaender, M.M., Kornberg, Z., Wald, H., Popovtzer, M.M.Renal effect of vitamin D metabolites: evidence for the essential role of the 25(OH) group. *Am. J. Physiol.* 1983; 244, F674–F678.

59. Kurnik, B.R., Hruska, K.A. Mechanism of stimulation of renal phosphate transport by 1,25-dihydroxycholecalciferol. *Biochim. Biophys. Act*, 1985; 817, 42–50.

60. Chase LR and Aurbach GD. Parathyroid function and the renal excretion of 3’5’-adenylic acid. *Proc Natl Acad Sci USA,* 1967; 58: 518–525.

61. Inoue, Y., Segawa, H., Kaneko, I., Yamanaka, S., *et al.*, 2005. Role of the vitamin D receptor in FGF23 action on phosphate metabolism. *Biochem. J*, 2005; 390, 325–331.

62. Shimada, T., Hasegawa, H., Yamazaki, Y., Muto, T., Hino, R., Takeuchi, Y., Fujita, T., Nakahara, K., Fukumoto, S., Yamashita, T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J. Bone Miner. Res*. 2004a; 19, 429–435.

63. Zhou C, Shi Z, Ouyang N, Ruan X. Hyperphosphatemia and Cardiovascular Disease. *Front Cell Dev Biol.* 2021; 9:644363.

64. Menon MC, Ix JH. Dietary phosphorus, serum phosphorus, and cardiovascular disease. *Ann N YAcad Sci* 2013; 1301:21-26.

65. Slatopolsky E. The intact nephron hypothesis: the concept and its implications for phosphate management in CKD-related mineral and bone disorder. *Kidney Int Suppl*. 2011 Apr;79(121): S3-8.

66. Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. *J Am Soc Nephrol.* 2010;21(9):1427-1435.

67. Hruska, K.A., Mathew, S., Lund, R., Qiu, P., Pratt, R. Hyperphosphatemia of chronic kidney disease. *Kidney Int.* 2008. 74, 148–157.

68. Craver, L., Marco, M.P., Martinez, I., Rue, M., Borras, M., Martin, M.L., Sarro, F., Valdivielso, J.M., Fernandez, E. Mineral metabolism parameters throughout chronic kidney disease stages 1-5-achievement of K/DOQI target ranges. *Nephrol. Dial. Transplant*. 2007; 22, 1171–1176.

69. Qunibi WY, Nolan CR. Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis: results of the CARE study. *Kidney Int Suppl*. 2004;(90): S33-S38.

70. https://www.businesswire.com/news/home/20210621005622/en/Hyperphosphatemia-Epidemiology-Forecast-Report-2021-2030---Research And Markets.com. Published date, June 21, 2021.

71. Moe S, Drüeke T, Cunningham J, *et al*. Definition, evaluation, and classification of renal osteodystrophy: a position statement from kidney disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2006;69(11):1945-1953.

72. Ganesh, S.K., Stack, A.G., Levin, N.W., Hulbert-Shearon, T., Port, F.K. Association of elevated serum PO (4), Ca x PO (4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J. Am. Soc. Nephrol*. 2001; 12, 2131–2138.

73. Verberckmoes SC, Persy V, Behets GJ, *et al*. Uremia-related vascular calcification: more than apatite deposition. *Kidney Int*. 2007; 71:298–303.

74. McGowan, J.P. Some considerations regarding and investigations into calcium and phosphorus metabolism. *Biochem. J*. 1933; 27, 934–942.

75. Velentzas, C., Meindok, H., Oreopoulos, D.G., Meema, H.E., Rabinovich, S., Sutton, D., Ogilvie, R. Detection, and pathogenesis of visceral calcification in dialysis patients and patients with malignant disease. *Can. Med. Assoc. J.* 1978; 118, 45–50.

76. Bellasi, A., Ferramosca, E., Ratti, C., Block, G., Raggi, P. Cardiac valve calcification is a marker of vascular disease in prevalent hemodialysis patients. *J Nephrol*, 2012; 25, 211–218.

77. Cozzolino M, Gallieni M, Brancaccio D. Vascular calcification in uremic conditions: new insights into pathogenesis. *Semin Nephrol*. 2006 Jan;26(1):33-37.

78. Slatopolsky E, Gonzalez E, Martin K. Pathogenesis and treatment of renal osteodystrophy. *Blood Purif*. 2003;21(4-5):318-326.

79. National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am. J. Kidney Dis*., 2000; 35, S1–140.

80. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am. J. Kidney Dis*, 2003; 42, S1–201.

81. Elseviers, M., de Vos, J.Y. The use of phosphate binders: data from contributors to the European Practice Database. *J. Ren. Care*, 2009; 35 (Suppl 1), 14–18.

82. Barreto FC, Barreto DV, Massy ZA, Drüeke TB. Strategies for Phosphate Control in Patients With CKD. *Kidney Int Rep*. 2019; 4(8):1043-1056.

83. Fissell RB, Karaboyas A, Bieber BA, *et al*. Phosphate binder pill burden, patient-reported non-adherence, and mineral bone disorder markers: findings from the DOPPS. *Hemodial Int*. 2016; 20:38–49.

84. Schilthuizen, S.F., Lawrence F., Baten B., Frank S., Franky F.V. Device for the removal of toxic substances from blood, 2015, Google Patents.

85. M.K. Kuhlmann. Phosphate elimination in modalities of hemodialysis and peritoneal dialysis *Blood Purification*, 29 (2010), pp: 137-144.

86. Ashurst Ide B, Dobbie H. A randomized controlled trial of an educational intervention to improve phosphate levels in hemodialysis patients. *Journal of Renal Nutrition*. 2003; 13:267-274.

87. Gutekunst L. An Update on Phosphate Binders: A Dietitian's Perspective. *J Ren Nutr*. 2016;26(4):209-218.

88. Ikizler TA, Burrowes JD, Byham-Gray LD, *et al*. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am J Kidney Dis*. 2003;42(4 Suppl 3): S1–S201.

89. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, *et al*. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(3):519-530.

90. Noori N, Sims JJ, Kopple JD, *et al*. Organic and inorganic dietary phosphorus and its management in chronic kidney disease. *Iran J Kidney Dis*. 2010;4(2):89-100.

91. Boaz M, Smetana S. Regression equation predicts dietary phosphorus intake from estimate of dietary protein intake. *J Am Diet Assoc*. 1996; 96:1268-1270.

92. Pecoits-Filho R. Dietary protein intake and kidney disease in Western diet. *Contrib Nephrol*. 2007; 155:102-112.

93. St-Jules DE, Goldfarb DS, Pompeii ML, Sevick MA. Phosphate Additive Avoidance in Chronic Kidney Disease. *Diabetes Spectr*. 2017;30(2):101-106.

94. Elder GJ, Malik A, Lambert K. Role of dietary phosphate restriction in chronic kidney disease. *Nephrology (Carlton).* 2018;23(12):1107-1115.

95. Uribarri J, Calvo MS. Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? *Semin Dial*. 2003; 16:186-188.
96. Dusek M, Kvasnicka F, Lukaskova L, *et al*: Isotachophoretic determination of added phosphate in meat products. *Meat Sci*, 2003; 65: 765-769.
97. Murphy-Gutekunst L. Hidden phosphorus: where do we go from here? *J Ren Nutr*. 2007; 17: e31-e6.
98. Bell RR, Draper HH, Tzeng DY, Shin HK, Schmidt GR. Physiological responses of human adults to foods containing phosphate additives. *J Nutr*. 1977; 107:42-50.
99. De Fornasari ML, Dos Santos Sens YA. Replacing Phosphorus-Containing Food Additives with Foods Without Additives Reduces Phosphatemia in End-Stage Renal Disease Patients: A Randomized Clinical Trial. *J Ren Nutr*. 2017;27(2):97-105.
100. National Center for Biotechnology Information. PubChem Compound Summary for CID 24203, Disodium hydrogen phosphate, Monosodium phosphate, Phosphoric acid, Sodium tripolyphosphate, Tetrasodium pyrophosphate, Trisodium phosphate, Dicalcium phosphate and Tricalcium phosphate. Accessed Aug. 1, 2022.
101. Melse-Boonstra A. Bioavailability of Micronutrients from Nutrient-Dense Whole Foods: Zooming in on Dairy, Vegetables, and Fruits. *Front Nutr.* 2020; 7:101.
102. Uribari J, Calvo MS: Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? *Semin Dial,* 2003*;* 16:186-188.

103. Watanabe MT, Araujo RM, Vogt BP, Barretti P, Caramori JCT. Most consumed processed foods by patients on hemodialysis: Alert for phosphate-containing additives and the phosphate-to-protein ratio. *Clin Nutr ESPEN*. 2016; 14:37-41.

104. Benini O, D'Alessandro C, Gianfaldoni D, Cupisti A. Extra-phosphate load from food additives in commonly eaten foods: a real and insidious danger for renal patients. *J Ren Nutr*. 2011;21(4):303-308.

105. Gutierrez OM, Anderson C, Isakova T, *et al*. Low socioeconomic status associates with higher serum phosphate irrespective of race. *J Am Soc Nephrol*. 2010; 21:1953–1960.

106. Ghidurus M, Turtoi M, Boskou M, Niculita P, Stan V. Nutritional and health aspects related to frying. *Rom Biotech Lett*. 2010; 15:5675-5682.

107. Burrowes ID, Ramer NJ. Changes in potassium content of different potato varieties after cooking. *J Ren Nutr*. 2008; 18:530-534.

108. Bethke PC, Jansky SH. The effects of boiling and leaching on the content of potassium and other minerals in potatoes. *J Food Sci*. 2008;73:H80-H85.

109. Yaseen AAE. Effect of processing conditions and cooking on retention of minerals in macaroni. *Food Nahrung*. 1993; 37:449-455.

110. Bognar A. Comparative study of frying to other cooking techniques influence on the nutritive value. *Grasas y Aceites*. 1998; 49:250-260.

111. Kimura M, Itokawa Y. Cooking losses of minerals in foods and its nutritional significance. *J Nutr Sci Vitaminol (Tokyo).* 1990; 36(suppl 1): S25-S32.

112. Ando S, Sakuma M, Morimoto Y, Arai H. The effect of various boiling conditions on reduction of phosphorus and protein in meat. *Journal of Renal Nutrition*, 2015;(25),6:504-509.

113. Vrdoljak I, Krbav I P, Bituh M, Vrdoljak T and Dujmi Z. Analysis of different thermal processing methods of foodstuffs to optimize protein, calcium, and phosphorus content for dialysis patients. *Journal of Renal Nutrition*, 2015;(25), 3:308-315.

114. Jones WL. Demineralization of a wide variety of foods for the renal patient. *J Ren Nutr* 2001; 11:90–96.

115. Picard K, Razcon-Echeagaray A, Griffiths M, Mager DR, Richard C. 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.* 2022; (22), 71-81.

116. Wang L, Wang J, Wang M, Li Y, Liang Y, Xu D. Using Internet search engines to obtain medical information: a comparative study. *J Med Internet Res*. 2012;14(3): e74.

117. Chen Y, Li C, Liang J, Tsai C. Health Information Obtained from the Internet and Changes in Medical Decision Making: Questionnaire Development and Cross-Sectional Survey. *J Med Internet Res* 2018;20(2): e47.

118. Smekal M, Gil S, Donald M, *et al*. Content and Quality of Websites for Patients with Chronic Kidney Disease: An Environmental Scan. *Can J Kidney Health Dis*. 2019; 6:2054358119863091.

119. Buettner K, Fadem SZ. The Internet as a tool for the renal community. *Advances in Chronic Kidney Disease.* 2008;15(1):73–82.

120. Fadem SZ, Walker DR, Abbott G, Friedman AL, Goldman R, Sexton S, Peters TG. Satisfaction with renal replacement therapy and education: The American Association of Kidney Patients survey. *Clinical Journal of American Society of Nephrology*. 2011;6(3):605–612.

121. Seto E, Cafazzo JA, Rizo C, Bonert M, Fong E, Chan CT. Internet use by end-stage renal disease patients. *Hemodialysis International*. 2007;11(3):328–332.

122. https://www.comscore.com/Insights/Rankings/comScore-Releases-February-2016-US-Desktop-Search-Engine-Rankings.

123. Jain A., "The Role and Importance of Search Engine and Search Engine Optimization", *International Journal of emerging trends & technology in computer science;*, 2013,(3); 2:99-102.

124. Al-Ubaydli M. Using Search Engines to Find Online Medical Information. *PLOS Medicine*, 2005; 2(9): e228.

125. https://totaldigitech.com/top-dominating-search-engines-in-the-market-share-worldwide-2021. Accessed Nov 2022.

126. Liu Y, Zhou XJ. Global Public Interest in CKD Based on Internet Searches. *Front Med (Lausanne).* 2021; 8:564967.

127. Garrido D, Watanabe A, Ciamponi AL, Couto TM, Alves LAC, Haddad AE. Patterns of Internet and smartphone use by parents of children with chronic kidney disease. *PLoS One.* 2019;14(2): e0212163.

128. Lutz ER, Costello KL, Jo M, *et al*. A systematic evaluation of websites offering information on chronic kidney disease. *Nephrol Nurs J*. 2014;41(4):355-364.

129. Kington RS, Arnesen S, Chou WS, Curry SJ, Lazer D, Villarruel AM. Identifying Credible Sources of Health Information in social media: Principles and Attributes. *NAM Perspect*. 2021;10.31478/202107a.

130. Smailhodzic, E., Hooijsma, W., Boonstra, A. *et al*. Social media use in healthcare: A systematic review of effects on patients and on their relationship with healthcare professionals. *BMC Health Serv Res*, 2016; 16, 442.

131. Jha A, Lin L, Savoia E. The use of social media by state health departments in the US: analyzing health communication through Facebook. *J Community Health* 2016;41(1):174-179.

132. Ormandy P. Defining information need in health - assimilating complex theories derived from information science. *Health Expect*. 2011;14(1):92-104.

133. Madathil KC, Rivera-Rodriguez AJ, Greenstein JS, Gramopadhye AK. Healthcare information on YouTube: a systematic review. *Health informatic journal*. 2015;21(3):173–94.

134. Ventola CL. Social media and health care professionals: benefits, risks, and best practices. *P T*. 2014;39(7):491-520.

135. Smith, A., & Anderson, M. Social media use in 2018: A majority of Americans use Facebook and YouTube, but young adults are especially heavy users of Snapchat and Instagram. https://www.pewresearch.org/internet/2018/03/01/social-media-use-in-2018.

136. Chung SY, Hacker ED, Rawl S, *et al*. Using Facebook in Recruiting Kidney Transplant Recipients for a REDCap Study. *West J Nurs Res*. 2019;41(12):1790-1812.

137. Vasilica CM, Brettle A, Ormandy P. A Co-Designed Social Media Intervention to Satisfy Information Needs and Improve Outcomes of Patients With Chronic Kidney Disease: Longitudinal Study. *JMIR Form Res*. 2020;4(1): e13207.

138. Ma T, Lambert K. What are the information needs and concerns of individuals with Polycystic Kidney Disease? Results of an online survey using Facebook and social listening analysis. *BMC Nephrol*. 2021;22(1):263.

139. Vasilica C, Oates T, Clausner C, Ormandy P, Barratt J, Graham-Brown M. Identifying Information Needs of Patients with IgA Nephropathy Using an Innovative social media-stepped Analytical Approach. *Kidney Int Rep*. 2021;6(5):1317-1325.

140. Goldstein K, Briggs M, Oleynik V, *et al*. Using digital media to promote kidney disease education. *Adv Chronic Kidney Dis*. 2013;20(4):364-369.

141. Moody EM, Clemens KK, Storsley L, Waterman A, Parikh CR, Garg AX. Improving on-line information for potential living kidney donors. *Kidney Int*. 2007;71(10):1062-1070.

142. Jaffery JB, Becker BN. Evaluation of eHealth web sites for patients with chronic kidney disease. *Am J Kidney Dis*. 2004;44(1):71-76.

143. Cai HC, King LE, Dwyer JT. Using the Google™ Search Engine for Health Information: Is There a Problem? Case Study: Supplements for Cancer. *Curr Dev Nutr*. 2021;5(2): nzab 002.

144. Smailhodzic E, Hooijsma W, Boonstra A, Langley DJ. Social media use in healthcare: A systematic review of effects on patients and on their relationship with healthcare professionals. *BMC Health Serv Res.* 2016;16(1):442.

145. Carter M. Medicine and the media: How Twitter may have helped Nigeria contain Ebola. *Br Med J*. 2014;349.

146. Welte AL, Harpel T, Schumacher J, Barnes JL. Registered dietitian nutritionists and perceptions of liberalizing the hemodialysis diet. *Nutrition Research and Practice*. 2019;13(4):310-315.

Chapter 2: Research study

A systematic review of online resources on dietary management of hyperphosphatemia in people with chronic kidney disease (CKD)

Introduction

People with chronic kidney disease (CKD) are at increased risk of cardiovascular disease (CVD), which is also the leading cause of death in this population. [1] One of the major CKD-specific factors driving the increased CVD risk in people with CKD is alterations in phosphorus metabolism, notably hyperphosphatemia [2], [3] In order to manage hyperphosphatemia, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in CKD: 2020 Update recommend lowering dietary phosphorus intake (1B). [4] However, specific dietary advice is limited to suggesting that treatment be individualized and take into account the differences in bioavailability of phosphorus by source. [4] Unfortunately, the field of renal nutrition is undergoing a paradigm shift [5], and renal dietitians appear to disagree on what should and should not be included in a low-phosphorus diet. [6], [7]

The Internet has become a key source of health information, dramatically increasing in use by the kidney disease community over the last decade. [8] Although search engines dominate online activity, social media websites have become a major platform where people can share and access health information. [9], [10] The benefits (and harms) of online resources to healthcare providers and patients depend on the accuracy of information, which is not safeguarded by peer review.

In the case of phosphate-specific diet therapy, the lack of specific advice in clinical practice guidelines, and consensus among renal dietitians presents an obvious potential for major inconsistencies and inaccuracies in information online. While inaccurate information can lead to direct harm, the harm from inconsistencies can be more insidious and far reaching, as inconsistent advice from reputable sources has the potential overwhelm, frustrate and demotivate patients, and cause them to question the merits and value of nutrition therapy. [5] Preliminary research based on Canadian healthcare websites suggests that advice for managing hyperphosphatemia is primarily focused on restrictions and is not entirely consistent across sources. [7] Given the homogeneity of the online sources in this study, it is likely that overall Internet sources are even more inconsistent. However, no previous study systematically evaluated online advice for phosphate-specific diet therapy. Therefore, the aim of this study is to summarize and evaluate the available online resources focused on dietary management of hyperphosphatemia in CKD patients.

Methods

Search strategy

Online resources were collected from the Google and Yahoo search engines and from the Facebook social media website. The first 100 hits were reviewed from nine independent searches. Search terms included combinations of “DIET” and “PHSOPHORUS” with: 1) “HYPERPHOSPHATEMIA”, 2) “HIGH BLOOD PHOSPHORUS”, “KIDNEY DISEASE”, “RENAL DISEASE”, “DIALYSIS”, “KIDNEY FAILURE”, “CHRONIC KIDNEY DISEASE”, “LOW” and “RESTRICTION”. Webpages were obtained over a two-week period from June to July 2021. In order to avoid the built-in algorithmic effects of Google, Yahoo and Facebook searches, the browsing history was erased by clearing browsing data and history, deleting cookies and cached files, and signing out of the platforms.

Inclusion and exclusion criteria

Online resources containing advice on phosphate-specific diet therapy were included for review. Resources that were unrelated (e.g., targeting animal), not patient-facing (e.g., research studies), or in languages other than English were excluded. Resources were examined independently and reviewed by two investigators for inclusion (MB, DES), and discrepancies were resolved by consensus.

Data extraction

Dietary advice was categorized according to food types, food groups, food sub-groups, and individual food items, as available and appropriate based on the level of detail provided in each resource. For each category, advice was classified as either recommended, restricted, or not mentioned. When conflicting advice were found within food categories from the same resource, the advice was considered mixed, and noted as both recommended and restricted. Findings for higher-level categories were incorporated from lower-level categories findings. For example, if meat was recommended in a resource, it was also categorized as a recommendation for animal-based protein foods. Any advice related food preparation methods (i. e., demineralization), phosphorus intake and bioavailability were also collected.

In addition to dietary guidance, publication information, including author credentials, website source, and date of publication or latest review were obtained.

Resources found in first 10 hits for each search term were considered as the most popular resources in Google and Yahoo, and number of "views" and "Likes" were considered as the indicator of popularity for the Facebook resources.

Statistical analysis

All statistical analysis were performed using SAS software, version 9.4 (SAS Institute Inc. 2013, Cary, NC) for Windows. Normality of continuous variables was assessed using the Shapiro-Wilk test and frequency distribution graphs, and the results were expressed as mean ± standard deviation for normally distributed continuous variables, and as median and interquartile range for non-normally distributed continuous variables. For categorical variables, values were presented as frequency (n/N) and percentages. Univariate associations between variables were assessed using Wilcoxon rank sum test, and Chi-square tests, as appropriate. Because of significant overlap in webpages, searches from Google and Yahoo were collapsed into one search engine group.

Results

Collected resources

Of the initial 1,800 resources obtained from search engine searches, 566 (31%) independent resources were available for analyses after removing duplicates (n=1,077 (60%)). Of 566 independent resources, after further excluding resources that were inaccessible (n=3 (0.5%)), not patient-facing (n=248 (44%)), and unrelated (n=116 (20%)), 199 (35%) unique resources were available for final review. **(Fig-2.1a)** In the initial search, 184 resources were obtained from Facebook. After removing duplicates (n=31 (17%)), 153 (83%) independent resources were identified, of which 120 (78%) were excluded for being irrelevant, leaving 33 (22%) resources for review. **(Fig-2.1b)**

From search engines

Dietary Advice

Dietary advice was primarily focused on restricting high-phosphorus foods rather than recommending low-phosphorus foods. Overall, roughly two-thirds (66%) of resources included lists of high-phosphorus foods to restrict compared to only 42% having lists of low-phosphorus foods to consume **(Table 2.1)**. Of different food types, processed foods were highly restricted (53%) **(Fig-2.2)**. For the major food groups and subgroups, the majority of resources suggested restricting dairy products (91%), animal-based and plant-based protein foods (81% and 71% respectively) and grain products (60%) **(Fig-2.3)**. Though they were rarely mentioned, fruits and vegetables were more likely to be recommended than restricted. Only 16 resources (8%) in search engines mentioned the demineralization as a strategy for reducing phosphorus intake (Table 2.1).

Among dairy products, low-fat foods were the most common target for restriction (82%) with milk being the most highly restricted food item in this food group (70%) **(Fig-2.4)**. Unlike fluid milk, plant-based alternatives such as soymilk were rarely mentioned (35%) and were more likely to be recommended than restricted. Noticeable mixed dietary advice was found for the cheeses (6%) with soft cheese being more likely to be restricted than hard cheese (50% vs 9%, respectively).

Animal- and plant-based protein foods were both targets for restriction. Of animal-based protein foods, meat and poultry products (52%), seafood (60%), and processed meat products (53%) were often restricted. Recommendations for eggs were rarely mentioned, and advice was notably mixed, as many resources promoted egg whites (13/199 (7%)). Plant-based protein foods were commonly restricted as a group, with similar proportions for legumes (68%), and nuts and seeds (68%).

Advice for grain products tended to encourage restricting whole grains (60%), and consuming refined grains (30%). However, many of the resources did not distinguish between whole and refined grains (30%). Of whole grain products, bran cereal (48%) was the food item most commonly restricted.

Recommendations and Bioavailability

Dietary phosphorus intake (mg/day) was suggested in 39 (20%) resources (Table 2.1). Bioavailability of phosphorus was also an important consideration in providing dietary advice in many of the resources. 32 (16%) of resources mentioned bioavailability of phosphorus for different food sources (plant = 45%, animal = 63%) and phosphorus additives (99%). However, bioavailability was specified for specific plant and animal-based proteins, dairy and phosphorus additives in many resources **(Fig-2.5)**

Source Information

Most of the resources came from websites (39%) and healthcare providers (29%), followed by non-government healthcare organizations (22%) and government healthcare organizations (4%). The vast majority of content were in the form of webpages and handouts (85%). Of all the resources collected from search engines, most popular were from healthcare providers, government and non-government healthcare organizations based on which resources from different publication sources were included in first ten finally reviewed resources for each search terms (**Table 2.2)**.

Registered dietitians were the leading authors (65%) of the resources in search engines though medical doctors authored a significant proportion of resources as well (31%). Authors were not specified in many of the resources (Table 2.1).

In comparative analysis, statistically significant results were obtained for authors providing dietary advice on processed foods and additives and advice on demineralization in search engines resources. 84% of registered dietitians suggested avoiding processed and additive-based foods and 56% by medical doctors, (*P*-value = 0.003). 12% of resources authored by registered dietitians suggested demineralization vs none of the handouts by medical doctors (*P*-value = 0.04).

From social media

The findings from the search of Facebook resources were broadly similar to the results from the search engines. A significant proportion of resources suggested restricting dairy products (70%), animal-based and plant-based protein foods (48% and 55%, respectively) and grain products (45%). **(Supplementary Fig-1)** In Facebook, non-government organizations (30%) and other sources like vlogs (42%) were the predominant sources. (Table 2.1) whereas all of the resources in Facebook were short videos (100%). (Table-2.1) However, in Facebook, medical doctors (57%) were the leading authors or the presenters in the short videos and registered dietitians covered a significant proportion (36%).

Discussion

This study provides a useful reference for defining phosphate-specific diet therapy, an issue of considerable debate in kidney nutrition. Overall, the findings suggest that people searching online would primarily encounter advice to restrict high-phosphorus foods, as well as processed foods containing phosphorus additives. Although restrictions for food groups and sub-groups overlapped considerably, there were notable inconsistencies, even though most resources reported being developed by registered dietitians and medical doctors, and often on behalf of reputable government and non-government healthcare organizations and providers. Considered together, the low-phosphorus diet appears to be highly restrictive, which could have important practical and nutritional consequences. In general, search engine resources tended to have more information than Facebook resources, which may be explained by the fact that most of the search engine resources were handouts /webpages that have more room to explain the dietary advice compared to short video formats in the Facebook.

Recently, a study evaluating low-phosphorus dietary advice from Canadian healthcare websites was published. [7] Similar to our findings, dietary advice focused on restricting phosphorus additive-based processed foods, whole grains, dairy products and processed meats, and included notable inconsistencies. [7] These issues appear to be mirrored in clinical practice. A cross-sectional study of 187 renal dietitians found that over half of the renal dietitians were more likely frequent in restricting inorganic phosphate-based foods than foods with organic phosphorus while many of them were not confident enough explaining what makes a low phosphorus diet. [6]

Most, but not all resources, recommended restricting plant-based protein foods and whole grains. The extent to which high-phosphorus plant foods were targeted was somewhat unexpected, as this conforms with more traditional concepts of the low-phosphorus diet and does not reflect the growing push for dietary liberalization, and the promotion of a whole food, plant-rich dietary pattern in this population. One of the main factors influencing this shift was the recognition that the majority of phosphorus in plant-based protein foods and whole grains is part of the storage compound phytate, which cannot be broken down by human digestive enzymes (i.e., lack phytase). [11] Although this issue was first introduced nearly two decades ago, it gained considerable traction after a landmark controlled feeding study by Moe *et al*. (2011) [12] provided the proof-of-concept. More recently, in free-living adults undergoing hemodialysis treatment, a pre-post clinical trial showed that daily consumption of almonds for four weeks was safe, effective, and well tolerated with no significant changes in the serum phosphorus level. [13] Plant-based foods are rich in dietary fibers along with other important nutrients and significant restriction can negatively impact CKD patients.

Generally, risk of hyperphosphatemia is higher in kidney failure patients. Because most of these patients are on dialysis, and there is a concern about protein-energy wasting (PEW) in this population, attempts to restrict animal sources of phosphorus have often been met with resistance, as they are major sources of high biologic value protein. Historically, the major focus had been on limiting dairy products but offsetting this restriction with additional servings of animal-based protein foods. [14] Consistent with historical dietary advice, dairy products were the highly restricted food group found in this study. However, animal-based protein foods were also common targets for restriction for managing hyperphosphatemia in people with CKD. When combined with restriction of plant-based protein foods, indicates a potential to reduce dietary balance, and therefore the nutritional adequacy of the diet. [6]

Processed foods containing phosphorus additives have become increasingly recognized as salient targets for reducing phosphorus intake without compromising diet quality based on their ubiquitous use, and relatively high bioavailability. Findings of this study showed that 53% resources targeted phosphorus additive-based processed foods for restriction. In contrast to restrictions on high-phosphorus animal and plant foods, which have not been studied in isolation for managing hyperphosphatemia, avoiding phosphorus additives have been demonstrated to lower serum phosphate levels in hemodialysis patients with persistent hyperphosphatemia, and without apparent negative effects on nutrition status.[15] [16] Although avoidance of phosphorus additives is arguably the most evidence-based for managing hyperphosphatemia, it is noteworthy that all resources reinforce the common myth that the inorganic phosphorus from food additives is almost completely absorbed into the body (90%-100% bioavailable). This inaccuracy stems from conflating digestibility with bioavailability. Although phosphorus additives are almost completely digested, the absorption of phosphorus is estimated to be about 70%-80% and may be even lower in the CKD population due to lower calcitriols levels. [17]

Demineralization or cooking loss has been shown to reduce the phosphorus content of foods substantially but was not often advised as a strategy in online resources. Several prior studies have reported phosphorus losses of up to 50%-70% from animal foods while largely maintaining protein contents.[1] [18] However, one of the key concerns with demineralization is that other water-soluble nutrients could be removed along with phosphorus. [19] Moreover, this method may not be appropriate for all phosphorus-based foods such as peanut butter, milk and cheese, limiting its utility. [20]

This study provides an overall picture of phosphate-specific diet therapy online from two popular search engines, and the social media website, Facebook. Unfortunately, too few resources were available from Facebook to allow meaningful comparative analyses between these two sources of information. One of the main problems in attempting to summarize and interpret the findings was the fact that resources differed in the level of dietary advice provided (food types, food groups, food subgroups vs individual food items), and often provided mixed advice, precluding generalizations. A major limitation of results was the fact that all resources was weighed equally, as it was not possible determine the relative popularity of websites.

Conclusion

This study summarized and explored the discrepancies in online resources providing dietary advice for managing hyperphosphatemia. Dietary guidance was primarily focused on restricting high-phosphorus foods than recommending low-phosphorus foods. In addition, substantial inconsistencies were found between resources. The findings of this study indicate an urgent need to establish a consistent consensus regarding phosphate-specific diet therapy for people with CKD. This study will help raise awareness about the quality of online dietary information for CKD patients and their caregivers.

Figure 2.1a. Flow chart of collecting resources from search engines (Google and Yahoo).

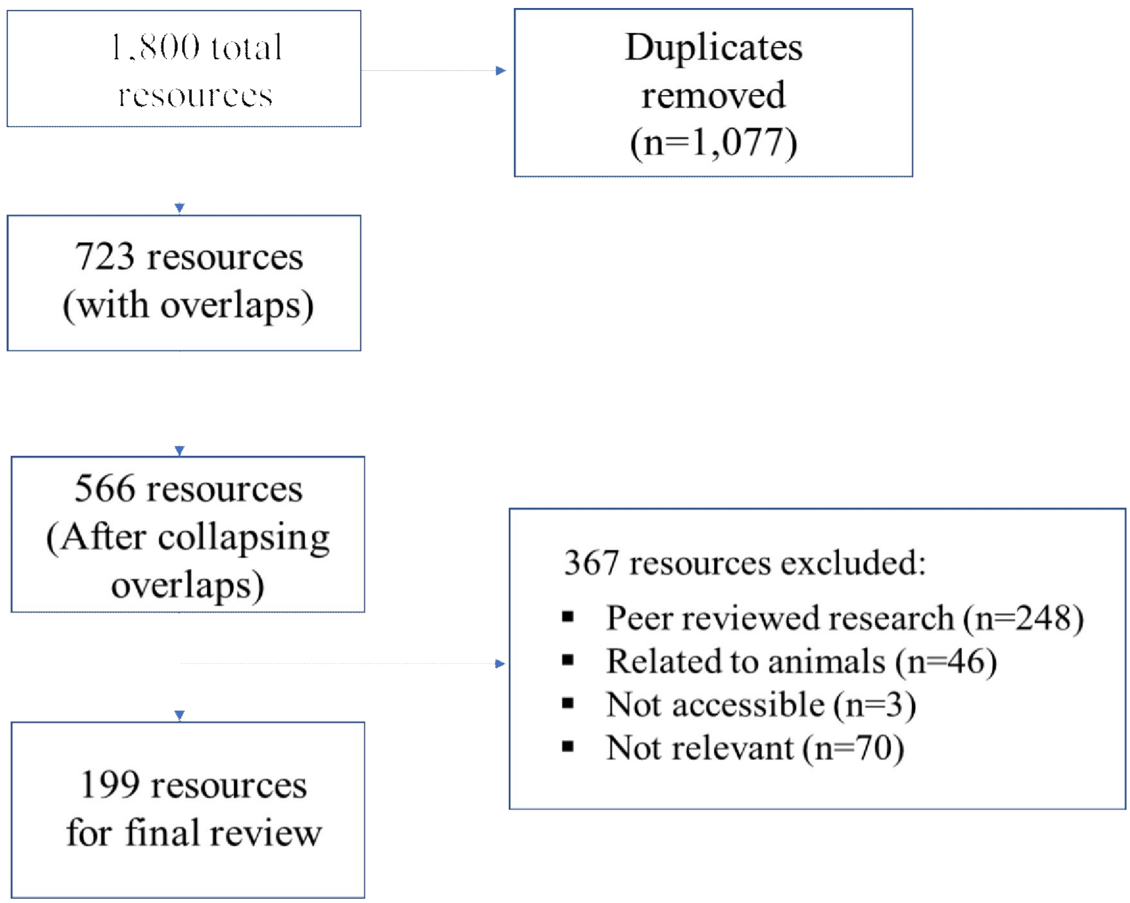


Figure 2.1b. Flow chart of collecting resources from social media (Facebook).

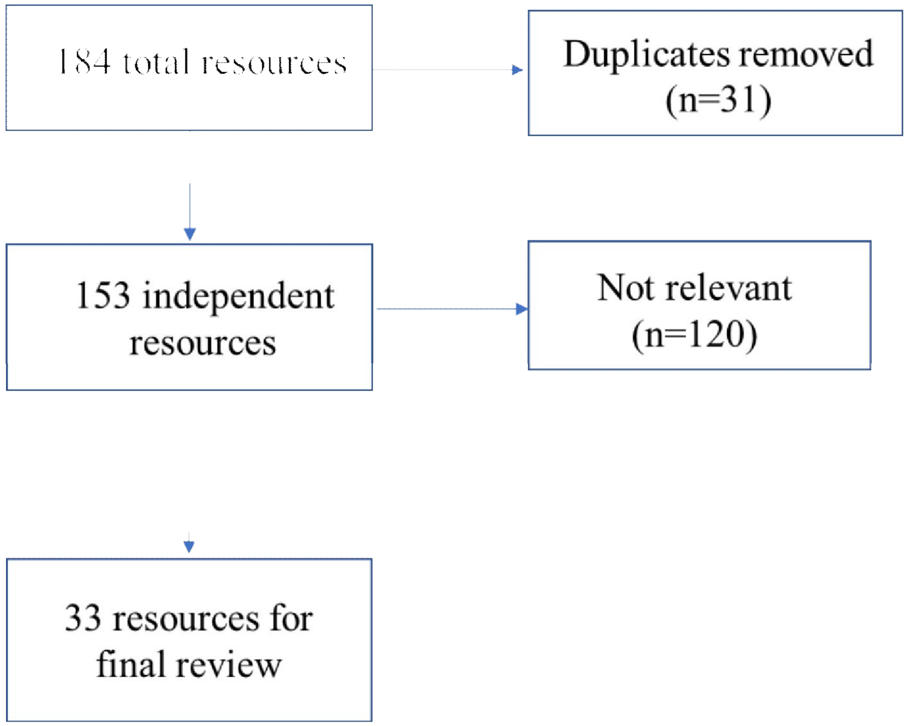


Figure 2.2. Dietary restrictions of food types in search engines and social media website.

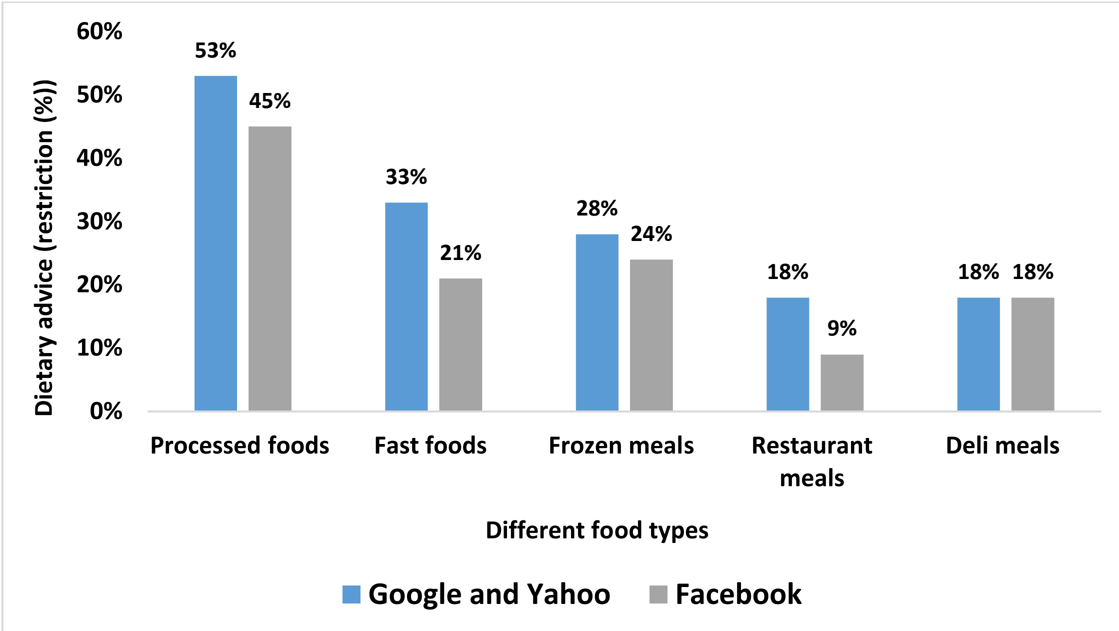
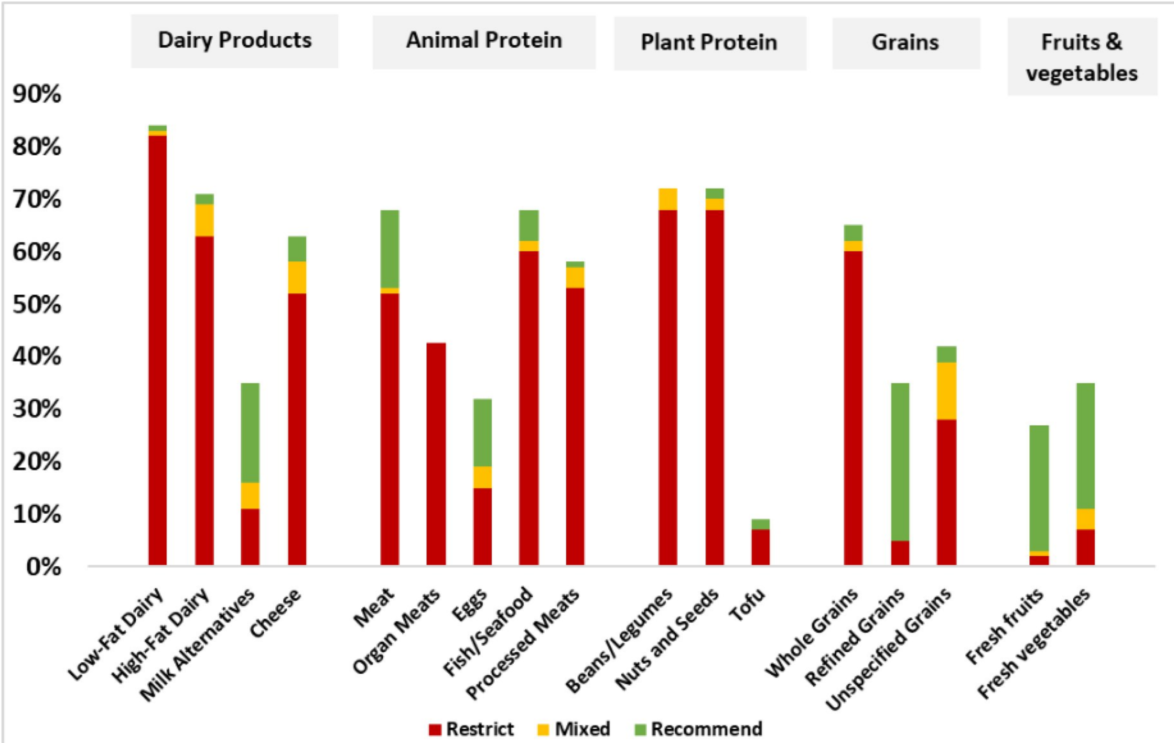


Figure 2.3. Dietary advice on key food groups and food sub-groups from search engines (Google and Yahoo).



Note: *Low-fat dairy includes- fluid milk, yogurt and Greek yogurt. High-fat dairy includes- cream soups, sour cream, whipping cream, and milkshakes. Milk alternatives includes- almond, rice and soy beverages. Cheese-based dairy includes-Soft Cheese (Brie, Ricotta, Cottage, Cream cheese) and Hard cheese (edam, mozzarella, Parmesan, cheddar, Colby).*

Meat includes- beef, poultry, turkey and pork. Fish/Seafood includes- seafood, fish, canned fish and shellfish. Processed meat includes- processed meats, enhanced meats, chicken nuggets, hot dogs, sausages and bacon.

Whole grains include- whole grain bread, pasta and crackers, brown and wild rice, oats, granola, bulgur, cornbread, whole grain and bran cereal, rice cakes and popcorn. Refined grains include- white, French and Italian bread, white and unfortified rice, corn, rice and refined grain cereal, pancakes, waffles and pretzels. Unspecified grains include- unspecified bread, quick bread, pasta, tortillas, biscuits, muffins and crackers.

Figure 2.4. Dietary advice (highly restricted vs lower recommended) on individual food items from search engine resources.

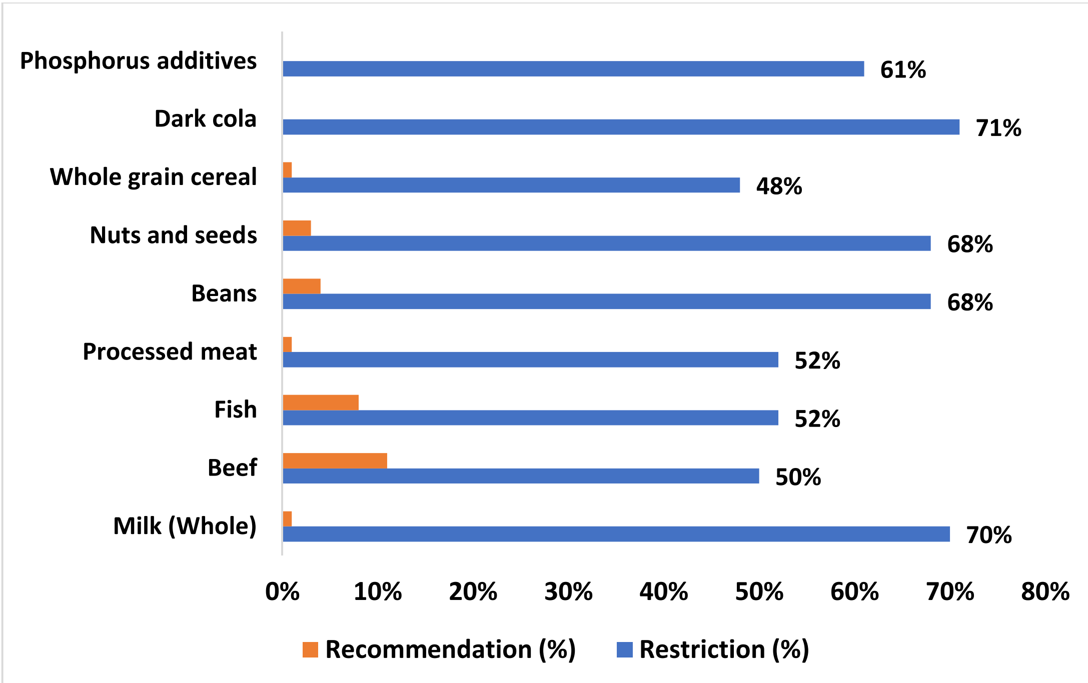


Figure 2.5. Bioavailability of phosphorus for different food sources in search engines resources.

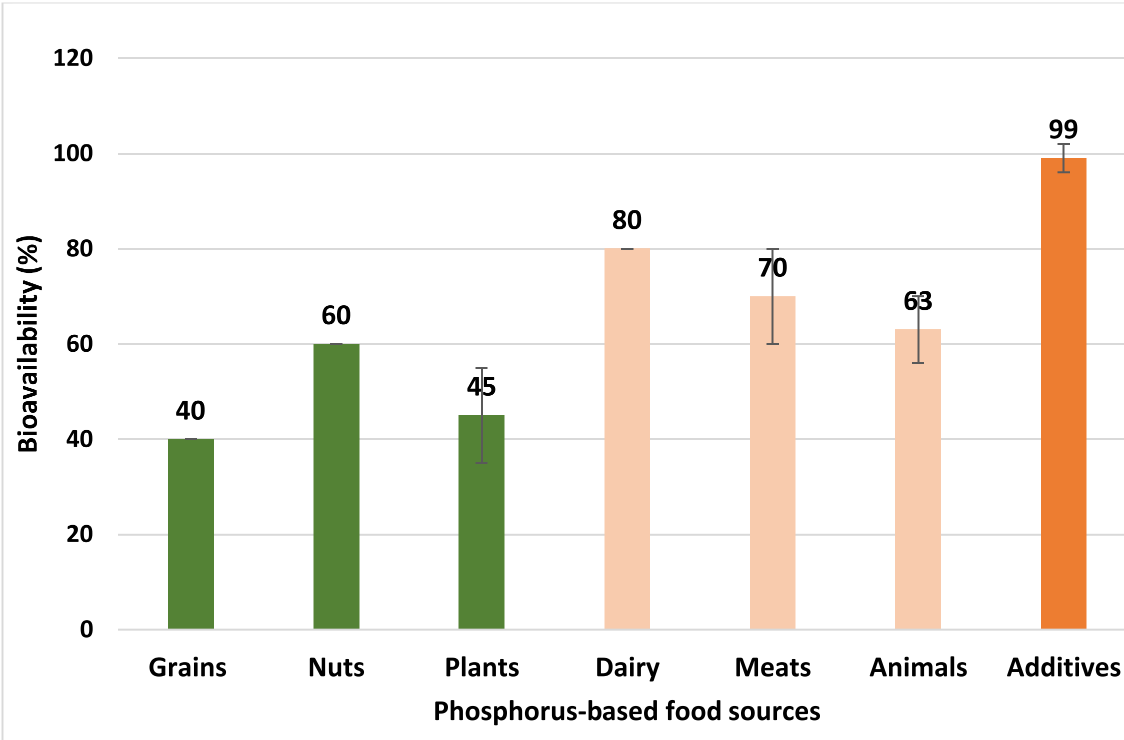


Table 2.1. Statistical analysis of variables of resources from search engines and social media on phosphate-specific diet therapy.

Variable	Google and Yahoo		Facebook	
	Value	n	Value	n
Publication Date (days)	706 (IQR = 187-1617) (7-4226)	133	572 (IQR = 397-973) (113-4270)	33
Proposed cutoff for hyperphosphatemia (mg/dL)	4.8 ± 0.5	40	5.5	1
Recommended Phosphorus (mg/d)	1018 ± 187	39	963 ± 151	8
Phosphorus specific (n (%))	107 (54)	199	18 (55)	33
Food List, Low-Phosphorus (n (%))	84 (42)	199	7 (21)	33
Food List, High-Phosphorus (n (%))	131 (66)	199	18 (55)	33
Publication Source (n (%))		199		33
Government	8 (4)		0	
Non-Government Organization	44 (22)		10 (30)	
Healthcare Provider	57 (29)		2 (6)	
Websites	77 (39)			
Other	11 (6)		21 (64)	
Publication Format (n (%))		199		33
Webpage/Handouts	170 (85)		-	
PowerPoint	4 (2)		-	
Video	7 (4)		33 (100)	
Other	18 (9)		-	
Author (n (%))		103	-	14
Registered Dietitian	67 (65)		5 (36)	
Medical Doctor	32 (31)		8 (57)	
Other	4 (4)		1 (7)	
Bioavailability (n (%))		199		33
Bioavailability of phosphorus	32 (16)			
Additives > Plant	24 (12)		1 (3)	
Additives > Animal	22 (11)		1 (3)	
Animal > Plant	12 (11)		2 (6)	
Demineralization (n (%))	16 (8)	199	5 (15)	33

Note: Values are presented as percentage (%) and mean ± SD for categorical and continuous variables, respectively.

Table 2.2. Sources of resources found in the first 10 hits from search engines (Google and Yahoo).

Resource providers	**Organizations vs websites**	**Frequency in first ten finally reviewed resources**
DaVita	Healthcare providers	4
NIDDK	Government	3
American Kidney Fund (AKF)	Non-government	3
NKF	Non-government	2
My Health.Alberta.ca	Government	1
Kidney Foundation	Non-government	1
Mayo Clinic	Healthcare providers	1
UNC Kidney Center	Healthcare providers	1
Cleaveland Clinic	Healthcare providers	1
Fresenius Kidney Care	Healthcare providers	1
Medical News Today	Website	1
Healthline	Website	1
Nutrients Review.com	Website	1
The Renal Tracker	Website	1
Doctor's Health Press.com	Website	1
Healthy Kidney Inc.com	Website	1

Supplementary Table 1. Dietary advice on key food groups, sub-groups and food items from both search engine (Google and Yahoo) resources.

Food categories/Sub-categories/Food items	**Dietary advice from search engines (Google + Yahoo) resources (Total=199)**						
	Recommended	**Restricted**	**Mixed advice**	**No advice**	**Recommended %**	**Restricted %**	**Mixed %**
Food types	**2**	**84**	**0**	**113**			
Processed food	0	105	0	94			
Fast food	0	65	0	134	**1%**	**42%**	**0%**
Canned food	0	19	0	180			
Frozen meals	2	56	0	141			
Restaurant foods	2	36	0	163			
Dairy products	**3**	**181**	**2**	**13**	**2%**	**91%**	**1%**
Low Fat Dairy products	**2**	**163**	**2**	**32**			
Milk (whole)	2	139	2	56	**1%**	**82%**	**1%**
Yogurt	1	79	1	118			
Greek yogurt	2	2	0	195			
High Fat Dairy Products	**11**	**126**	**4**	**58**			
Cream cheese	31	1	1	166			
Cream soup	1	28	2	168			
Sour cream	14	2	0	183			
Ice-cream	3	75	0	121	**6%**	**63%**	**2%**
Custard/pudding	2	62	0	135			
Butter/margarine	22	0	0	177			
Whipping cream	5	0	0	194			
Milk shake	1	13	0	185			
Milk alternatives	**37**	**22**	**11**	**129**			
Soy milk	19	18	0	162			
Almond milk	20	2	0	177	**19%**	**11%**	**6%**
Rice milk	41	4	0	154			
Cheese-based dairy	**10**	**104**	**12**	**73**			

Soft Cheese (Brie, Ricotta, Cottage, Cream cheese)	21	100	0	78	**5%**	**52%**	**6%**
Hard cheese (edam, mozzarella, Parmesan, cheddar, Colby)	6	17	0	176			
Animal protein food	**29**	**103**	**3**	**64**	**15%**	**52%**	**2%**
Meat-based protein	**20**	**99**	**1**	**79**	**10%**	**50%**	**0%**
Beef	20	99	1	79			
Poultry/chicken	27	62	1	109			
Turkey	23	21	0	155			
Pork	19	19	0	161			
Egg-based protein	**25**	**30**	**9**	**135**	**13%**	**15%**	**5%**
Egg	24	30	0	145			
No egg but egg white	12	0	0	187			
Egg white only	1	0	0	198			
Fish-based protein	**12**	**119**	**5**	**63**	**6%**	**60%**	**3%**
Fish	15	104	0	80			
Canned fish	1	51	0	147			
Seafood	3	28	0	168			
Shellfish	5	53	0	141			
Organ meats	**0**	**85**		**114**	**0%**	**43%**	**0%**
Processed meat foods	2	106	7	83	**1%**	**53%**	**4%**
Processed Meats	1	104	0	94			
Enhanced Meats	9	32	0	158			
Chicken nugget	0	13	0	186			
Hot dog/sausage	3	31	0	165			
Bacon	0	16	0	183			
PBPF (Plant based protein food)	**6**	**141**	**10**	**42**	**3%**	**71%**	**5%**
Beans/legumes	8	135	1	55			
Nuts/seeds	6	136	4	**55**			

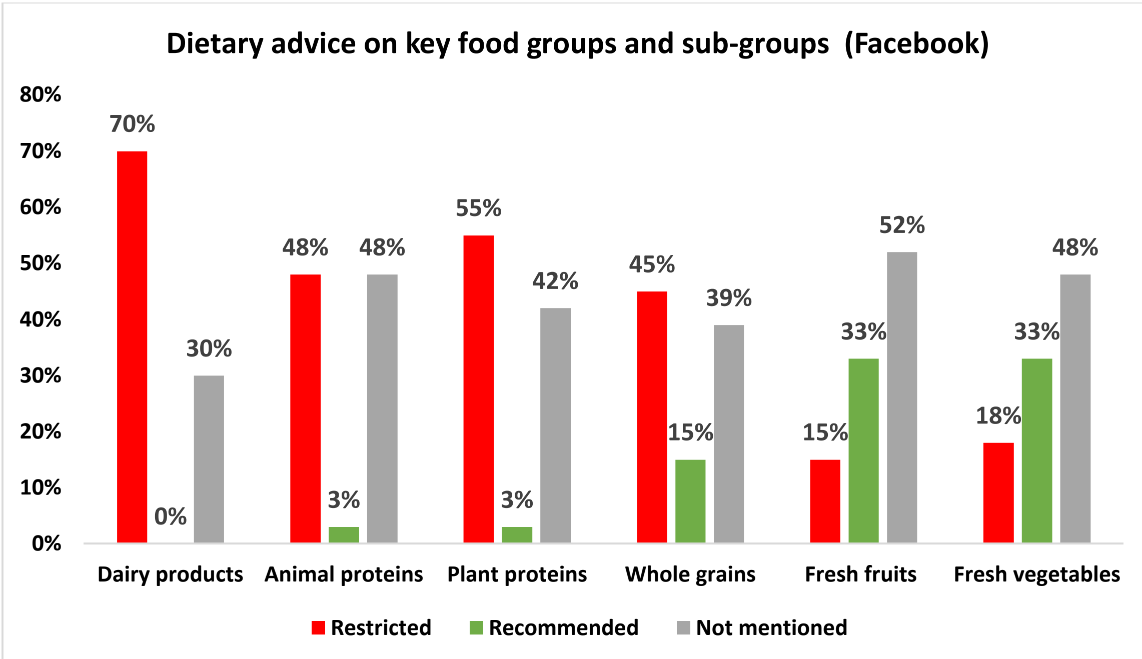
Tofu	5	13	0	181			
P. additives	**0**	**122**		**77**	**0%**	**61%**	**0%**
Beverages							
Beverages (With additives)	**0**	**150**	**4**	**45**	**0%**	**75%**	**2%**
Dark cola	0	141	0	58			
Energy/sport drinks	0	22	0	177			
Beer/ale	0	62	0	137			
Wine	5	17	0	177			
Cocoa/chocolate drinks	0	63	0	136			
Chocolate milk	0	29	0	170			
Canned iced tea	0	61	0	138			
Fruit punch	0	20	0	179			
Bottled water	0	16	0	183			
Flavored drinks	1	40	0	158			
Beverages (without additives)	**75**	**5**	**1**	**118**	**38%**	**3%**	**0%**
Light cola	51	1	0	147			
Root beer	37	2	0	160			
Ginger ale	23	4	0	172			
Water	15	0	0	184			
Coffee	25	0	0	174			
Homemade tea	31	0	0	168			
Hot apple cider	8	0	0	191			
Lemonade	36	0	0	163			
Fruit juice	19	0	0	180			
Grains	**6**	**119**	**4**	**70**	**3%**	**60%**	**2%**
Whole grains	**6**	**119**	**4**	**70**	**3%**	**60%**	**2%**
Whole G Bread/Whole wheat bread	1	54	0	144			
Oats	0	51	0	148			
Whole grain pasta	1	22	0	176			
Whole grain/bran cereal	1	96	0	102			
Whole grain crackers	0	16	0	183			

Bulgar	6	6	0	187			
Wild rice	0	22	0	177			
Brown rice	2	37	0	160			
Refined grains	**59**	**9**	**1**	**130**	**30%**	**5%**	**0%**
Corn/rice/refined wheat cereal	43	2	0	154			
White/French/Italian bread	33	2	0	164			
White pasta	23	1	0	175			
Rice/white rice	34	0	0	165			
Tortillas (Flour)	2	5	0	192			
Refined grain crackers	17	2	0	180			
Refined grain goods	8	0	0	191			
Unspecified grain products							
Macaroni	1	12	0	186			
Pancake/waffles	1	41	0	157			
Muffin	7	34	0	158			
Pizza	2	21	0	176			
Baked goods	0	39	0	160			
Biscuits	4	32	0	163			
Quick bread	3	20	0	176			
Crackers	17	4	0	178			
Cake	16	13	0	170			
Cookies	11	8	0	180			
Cornbread	0	16	0	183			
Rice cake	8	1	0	190			
Donut	3	5	0	191			
Pasta	13	9	0	177			
Fresh Fruits	**48**	**3**	**146**	**2**	**24%**	**2%**	**1%**
Apples	14	1	0	184			
Berries	16	0	0	183			
Grapes	12	0	0	187			
Peaches	6	1	0	192			
Apricots	4	1	0	194			
Pineapple	8	0	0	191			
Coconut	3	0	0	196			
Lychee	1	1	0	197			
Raisin	0	4	0	195			
Dates	0	2	0	197			

Tamarind	0	1	0	198			
Dried fruits	10	4	0	185			
Fresh vegetables	**47**	**14**	**130**	**8**			
Salad dressings	2	3	0	194			
Carrot	10	0	0	189			
Brussels sprout	2	3	0	194			
Green beans/wax beans	18	1	0	180			
Avocado	0	7	0	192			
Spinach	1	4	0	194			
Green leafy vegetables	12	1	0	186			
Cabbage	6	0	0	193			
Cucumber	8	0	0	191			
Eggplant	2	0	0	197			
Okra	2	0	0	197			
Sweet potato	2	4	0	193			
Cauliflower	8	0	0	191	**24%**	**7%**	**4%**
Radish	3	0	0	196			
Turnip	2	1	0	196			
Broccoli	4	7	0	188			
Bell pepper	4	1	0	194			
Arugula	2	0	0	197			
Mushroom	1	13	0	185			
Corn	6	7	0	186			
Artichoke	1	3	0	195			
Heart of palm	0	1	0	198			
Lotus root	0	1	0	198			
Asparagus	8	3	0	188			
Pumpkin	3	4	0	192			
Squash	5	1	0	193			
Others							
Jam	22	0	0	177			
Jelly/gelatin dessert	16	2	0	181			
Honey	17	0	0	182			
Jell-o	13	6	0	180			
Artificial sweeteners	1	1	0	197			
Vinegar	2	0	0	197			
Tahini	0	3	0	196			
Mayonnaise	1	1	0	197			
Soup/pea soups	1	6	0	192			

Broth soup	7	0	0	192			
Snack products	0	4	0	195			
Chocolate	**0**	**62**	0	137	**0%**	**31%**	**0%**
Preservatives	0	5	0	194			
Caramel	1	22	0	176			
Syrup	1	1	0	197			
Yeast	2	11	0	186			
Candy/treats/Jellybean	21	4	0	174			
Fruit Snacks/fruit candy	0	13	0	186			
Rice crisps	10	2	0	187			

Supplementary Figure 1. Dietary advice on key food groups, sub-groups from Facebook resources.



References

1. Ando S, Sakuma M, Morimoto Y, Arai H. The effect of various boiling conditions on reduction of phosphorus and protein in meat. *Journal of Renal Nutrition*, 2015; (25), 6: 504-509.

2. Zhou C, Shi Z, Ouyang N, Ruan X. Hyperphosphatemia and Cardiovascular Disease. *Front Cell Dev Biol*.2021; 9:644363.

3. Shaman AM, Kowalski SR. Hyperphosphatemia Management in Patients with Chronic Kidney Disease. *Saudi Pharm J*. 2016; 24(4):494-505.

4. Ikizler TA, Burrowes JD, Byham-Gray LD, *et al*. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update [published correction appears in American Journal of Kidney Disease. 2021 Feb;77(2):308]. *American Journal of Kidney Disease*. 2020;76(3 Suppl 1): S1-S107.

5. St-Jules DE, Fouque D. Is it time to abandon the nutrient-based renal diet model? *Nephrol Dial Transplant.* 2021;36(4):574-577.

6. Welte AL, Harpel T, Schumacher J, Barnes JL. Registered dietitian nutritionists and perceptions of liberalizing the hemodialysis diet. *Nutrition Research and Practice.* 2019;13(4):310-315.

7. Picard K, Razcon-Echeagaray A, Griffiths M, Mager DR, Richard C. 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*. 2022; S1051-2276(22)00071-1

8. Smekal M, Gil S, Donald M, *et al.* Content and Quality of Websites for Patients with Chronic Kidney Disease: An Environmental Scan. *Can J Kidney Health Dis*. 2019; 6:2054358119863091.

9. Lutz ER, Costello KL, Jo M, *et al.* A systematic evaluation of websites offering information on chronic kidney disease. *Nephrol Nurs J.* 2014;41(4):355-364.

10. Chung SY, Hacker ED, Rawl S, *et al*. Using Facebook in Recruiting Kidney Transplant Recipients for a REDCap Study. *West J Nurs Res*. 2019;41(12):1790-1812.

11. Uribarri J, Calvo MS. Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? *Semin Dial.* 2003; 16:186-188.

12. Moe SM, Zidehsarai MP, Chambers MA, *et al.* Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clinical Journal of American Society of Nephrology.* 2011;6(2):257-264.

13. Lambert K, Bird L, Borst AC, *et al.* Safety and Efficacy of Using Nuts to Improve Bowel Health in Hemodialysis Patients. *Journal of Renal Nutrition*. 2020;30(5):462-469.

14. St-Jules DE, Fouque D. Is it time to abandon the nutrient-based renal diet model? *Nephrol Dial Transplant.* 2021;36(4):574-577.

15. Sullivan C, Sayre SS, Leon JB, *et al*. Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. *JAMA*. 2009;301(6):629-635.

16. De Fornasari ML, Dos Santos Sens YA. Replacing Phosphorus-Containing Food Additives with Foods Without Additives Reduces Phosphatemia in End-Stage Renal

Disease Patients: A Randomized Clinical Trial. *Journal of Renal Nutrition*. 2017;27(2):97-105.

17. Ramirez JA, Emmett M, White MG, *et al.* The absorption of dietary phosphorus and calcium in hemodialysis patients. *Kidney Int.* 1986;30(5):753-759.

18. Cupisti A, Comar F, Benini O, *et al.* Effect of boiling on dietary phosphate and nitrogen intake. *Journal of Renal Nutrition*. 2006;16(1):36-40.

19. St-Jules DE, Goldfarb DS, Pompeii ML, Sevick MA. Phosphate Additive Avoidance in Chronic Kidney Disease. *Diabetes Spectr*. 2017;30(2):101-106.

20. Jones WL. Demineralization of a wide variety of foods for the renal patient. *J Ren Nutr* 2001; 11:90–96