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Relationships Of Dietary Protein And Phosphorus With Protein Energy Wasting In Hemodialysis Patients

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RELATIONSHIPS OF DIETARY PROTEIN AND PHOSPHORUS WITH PROTEIN ENERGY WASTING IN HEMODIALYSIS PATIENTS

by

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DEDICATION

I dedicate this thesis to my husband, Steve, whose selflessness made it possible for me to complete this work, and to our children, Emily and Mark, who provided unconditional encouragement and support.

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LIST OF ABBREVIATIONS AND ACRONYMS

BIA: BioImpedance Analysis

BMI: Body Mass Index

CKD: Chronic Kidney Disease

CKD-MBD: Chronic Kidney Disease-Mineral and Bone Disorder

CRS: Cardio Renal Syndrome

CVD: Cardiovascular disease

DEI: Dietary Energy Intake

DPI: Dietary Pro Intake

eGFR: Estimated Glomerular Filtration Rate

ESRD: End Stage Renal Disease

FGF-23: Fibroblast growth factor-23

GIT: Gastro Intestinal Tract

HD: Hemodialysis

HDL-C: High-Density Lipopro Cholesterol

HGS: Hand Grip Strength

KDIGO: Kidney Disease Improving Global Outcomes

KDOQI: Kidney Disease Outcomes Quality Initiative

LDL-C: Low-Density Lipopro Cholesterol

MAC: Mid-upper Arm Circumference

MAMC: Mid Arm Muscle Circumference

MAMA: Mid Arm Muscle Area

MHD: Maintenance Hemodialysis

NHANES: National Health and Nutrition Examination Survey

NKF: National Kidney Foundation

nPCR: Normalized Pro Catabolic Rate

nPNA: Normalized Pro Nitrogen Appearance

PEW: Pro Energy Wasting

Phosphorus: P

PTH: Parathyroid Hormone

Protein: pro

QOL: Quality of Life

RRT: Renal Replacement Therapy

TSF: Triceps Skin Fold

USRDS: United States Renal Data System

Chapter I: Introduction

In a cohort study of 224 maintenance hemodialysis (MHD) patients, Noori, et al. found that both a higher dietary intake of phosphorus (P) and a ratio of higher P to protein (pro) intake were associated with increased mortality risk in hemodialysis (HD) patients.[1] Furthermore, dietary P restriction to control serum P is usually tied to a reduction in pro intake, which is associated with muscle wasting and poor survival.[2] One highly prevalent complication of end stage renal disease is protein energy wasting (PEW), a state of decreased body protein stores and fat mass, which is strongly associated with increased morbidity and mortality in the hemodialysis (HD) population.[3] The purpose of this study was to analyze the extent to which diet composition is associated with PEW parameters (serum chemistry, body mass, muscle mass, and dietary intakes).

It was hypothesized that the patients whose diets contained the lowest P/pro ratio would demonstrate the fewest clinical indicators of PEW. Results from this and future studies may help in designing diets to minimize PEW in the HD population.

As part of an initial screening phase for a collaborate multi-centered interventional clinical trial involving HD patients from both Michigan (United States) and Selangor (Malaysia), data was collected from several HD clinics in Klang Valley, an area in Malaysia centered in Kuala Lumpur. The diverse ethnic population is this area, comprised of Indian, Malay, and Chinese patients, differs vastly from the predominately African American patient pool found in Michigan. To the best of our knowledge, this is the first study to assess the relationship between the ratio of P/pro intakes and measures of PEW in a group of Malaysian MHD patients.

CHAPTER II: REVIEW OF LITERATURE

Chronic kidney disease and end-stage renal disease

According to the United States Renal Data System (USRDS), a surveillance system that collects, analyzes, and reports information about chronic kidney disease and end-stage renal disease (ESRD) in the United States, there were 661,648 prevalent cases of ESRD in the U.S. in 2013, an increase of 68% since 2000. [4] The Malaysian Society of Nephrology also maintains a registry of dialysis patients, reporting annually on ESRD trends. Malaysia has experienced a similar rise in the number of prevalent dialysis patients, with a 63% increase from 2005 to 2014. [5] Long-term survival on dialysis remains poor, with a 54% survival rate after five years of ESRD onset in Malaysia and after three years in the United States. [6; 7] Cardiovascular disease (CVD) comorbidity, reported at ten to thirty times higher in CKD patients as compared to the general population, partially explains increased mortality rates observed with CKD. In Malaysia, CVD related comorbidity accounted for 37% of all deaths for ESRD patients in 2014. [7] This interrelationship of CKD and CVD metabolic derangements is referred to as cardiorenal (CRS) syndrome. The underlying pathophysiologies in CRS include a myriad of hormonal, hemodynamic, and CKD related factors, such as inflammation, calcium-phosphate imbalance, and anemia.[8]

In both the United States and Malaysia, diabetes is the principal cause of CKD, followed by hypertension. Types of renal replacement therapy (RRT) that replace the non-endocrine functions of the kidney include dialysis (both hemodialysis and peritoneal) hemofiltration, and hemodialfiltration. While a kidney transplant, regarded as the gold standard in RRT,

does restore regulatory hormones, abnormalities of bone and mineral metabolism persist in most patients. [9]

Protein Energy Wasting

The term protein energy wasting (PEW), characterized by a loss of body pro mass and fuel reserves, was proposed by the International Society of Renal Nutrition and Metabolism (ISRNM) in 2007. Etiologies of PEW include multiple factors that affect nutrient metabolism, as outlined in **Table 1**.

Table 1

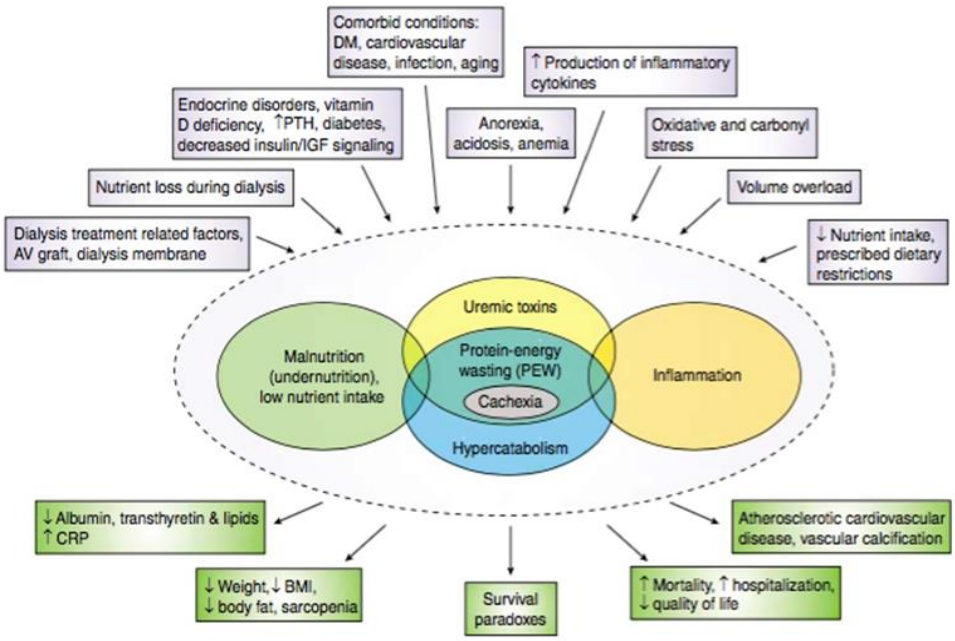
Causes of PEW
Decreased Nutrient Intake
Anorexia
Dietary Restrictions
Depression
Obstacles to food purchases/preparation
Decreased physical activity
Endocrine/Hormonal Dysfunction
Insulin Resistance
Decreased insulin-like growth factor-1
Vitamin D deficiency
Hyperparathyroidism
Increased pro catabolism
Decreased anabolism
Inflammation
Oxidative and carbonyl stress
Metabolic acidosis
Volume overload
Comorbidities
Diabetes
CVD
Congestive heart failure
Nutrient losses during dialysis

[3]

The pathophysiology of PEW is complex and involves overlapping mechanisms as depicted in **Figure 1** [3; 10; 11] Estimated prevalence of PEW ranges from twenty to fifty percent, with higher rates observed during the later stages of CKD due to activation of pro-inflammatory cytokines, hypercatabolic states and declines in nutrient intakes.[12]

Figure 1

Schematic representation of the causes and manifestations of the pro–energy wasting syndrome in kidney disease



Reprinted from reference [11]

PEW has been associated with higher morbidity and mortality and poorer quality of life (QOL) in ESRD patients. [13] Four clinical indicators proposed by the ISRNM for the diagnosis of PEW in CKD are outlined in **Table 2**. PEW is evident if criteria for at least three of the four categories [serum chemistry, body mass index (BMI), muscle mass, and dietary intake] are met.[3]

Table 2
Criteria for the clinical diagnosis of pro-energy wasting in chronic kidney disease

Serum Chemistry	Serum albumin <3.8 g/dl[a] Serum prealbumin (transthyretin) <30 mg/dl (for maintenance dialysis patients only)[a] Serum cholesterol <100 mg/dl[a]
BMI	BMI (edema-free) <23[b] Unintentional weight loss over time: 5% over 3 months or 10% over 6 months Total body fat percentage <10%
Muscle Mass	Reduced muscle mass 5% over 3 months or 10% over 6 months Reduced mid-arm muscle circumference area[c] (reduction >10% in relation to 50th percentile of reference population) Creatinine appearance[d]
Dietary Intake	Unintentional low dietary pro intake <0.80 g/kg/day for at least 2 months for dialysis patients or <0.6g/kg/day for patients with CKD stages G2–5 Unintentional low dietary energy intake <25 kcal/kg/day for at least 2 months

[a]Not valid if low concentrations are due to abnormally great urinary or gastrointestinal pro losses, liver disease, or cholesterol-lowering medicines
[b]A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, post-dialysis dry weight.
[c]Measurement must be performed by a trained anthropometrist
[d]Creatinine appearance is influenced by both muscle mass and meat intake
[d]Can be assessed by dietary diaries and interviews, or for pro intake by calculation of normalized pro equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements.[(11)]

PEW Criteria

1. *Serum chemistry*

Albumin

Hypoalbuminemia is a strong predictor of both cardiovascular and all-cause mortality in all stages of CKD. In the Nutritional and Inflammatory Evaluation in Dialysis Study, an observational analysis of over 3000 maintenance HD patients, both a low normalized protein nitrogen appearance (nPNA), a surrogate for dietary pro intake, and an

inflammatory state were associated with low serum albumin.[14; 15] It was noted that nPNA, a measurement of net pro degradation calculated using several dialysis parameters, might overestimate dietary pro intake due to catabolism of endogenous nitrogen in states of inflammation. [16] Albumin, a negative acute phase reactant, has been criticized as a reliable marker of malnutrition. Albumin is a water-soluble negatively charged pro synthesized in the liver. Functions include maintaining oncotic pressure, modulating coagulation by preventing platelet aggregation, binding free radicals and bacterial toxins and heavy metals, and transporting molecules such as fatty acids, thyroid hormones, steroids, bilirubin, calcium, and magnesium in plasma. [17] Serum levels of albumin fall due to fluid overload, infection, and inflammation, which trigger mechanisms leading to increased degradation and reduced production. Many dialysis clinics use albumin level as a qualitative rationale for supplement use, placing unsupported importance on this marker as an indicator of malnutrition. Albumin may preferably be utilized as a marker underlying illness and inflammation.[18; 19; 20]

Serum Cholesterol

Hypercholesterolemia in the general population is a known cardiovascular risk factor; however, within the HD population an inverse association of total cholesterol with mortality is observed. Dyslipidemia in CKD, which may be indicated by elevated plasma cholesterol, hypertriglyceridemia, high lipoprotein(a) [Lp(a)], low high-density lipoprotein cholesterol (HDL-C) or dysfunctional HDL particles is highly prevalent in ESRD patients. Elevated low-density lipoprotein cholesterol (LDL-C), and thus total cholesterol, is not a distinct characteristic of uremic dyslipidemia. Reduction in LDL-C in patients not taking

lipid-lowering medication may be the result of inflammation and malnutrition. Furthermore, although serum LDL-C may not be elevated, this lipoprotein is often modified by oxidation and carbamylation with an increase in the proportion of small dense LDL (sdLDL) subtype. [21; 22; 23]

2. Body Mass Index (BMI)

Whereas normal weight BMI within a healthy population is associated with a lower all-cause mortality risk, a higher BMI improves survival in both CHD, heart failure and dialysis patients.[24; 25] This phenomenon is known as the "obesity paradox" or "reverse epidemiology." [15; 26] However, this survival advantage for cardiovascular mortality within the HD population is lost in the presence of inflammation, as indicated by both CRP and albumin levels.[27] It is speculated that a higher lean body mass, not fat mass, is responsible for the protective effects observed within the higher BMI groups.[25]

3. Muscle Mass

Anthropometric measures of skeletal muscle mass are an indirect assessment of muscle protein. Since about sixty percent of total body protein is located in skeletal muscle, muscle wasting may indicate a loss of muscle protein in response to poor nutritional intake. Anthropometric measurements used to estimate muscle mass include triceps skinfold thickness (TSF), an estimation of body fat, mid-upper arm circumference (MAC), and mid-arm muscle area (MAMA) or mid-arm muscle circumference (MAMC), a formula which indirectly estimates muscle mass (see **Table 3**). TSF is a measurement taken using calipers at the mid-line on the posterior surface of the arm over the triceps muscle. MAMC

is a calculated measurement derived from deducting TSF from mid-upper arm circumference. An arm muscle area equation that corrects for bone area can provide a more accurate assessment of bone-free muscle area; however, the corrected equation is neither validated for elderly patients, nor appropriate for use in obese individuals. [28] Using the non-fistula arm, three measurements of TSF and MAC are typically taken after dialysis, and either the average or highest value is used for comparison to standard percentiles of a reference population (e.g. NHANES I). Efforts have been made to develop standardized MAMC tables specific to the hemodialysis population. A higher MAMC, an indicator of lean body mass, and higher TSF, an indicator of fat mass, have each been associated with a decrease in mortality in hemodialysis patients. [29; 30]

Table 3 [31]

Mid arm fat area (AFA)	AFA (cm2) = $\frac{MAC\ (cm) x\ TSF(cm)}{2} - \frac{\pi\ x\ (TSF)^2}{4}$
Mid arm muscle circumference area (MAMA)	MAMA (cm2) = $\frac{[MAC\ (cm) - (\pi\ x\ TSF)]^2}{4\pi}$
Mid-arm muscle Circumference (MAMC)	MAMC (cm) = MAC (cm) – $[\pi\ x\ TSF\ (cm)]$
Body frame size is determined by a person's wrist circumference in relation to his height (https://www.nlm.nih.gov/medlineplus/ency/imagepages/17182.htm)	

Values less than the 5th percentile for both arm muscle area and arm fat area indicate severe depletion. Values between the 5th and 10th percentiles for both arm muscle area and arm fat area represent moderate depletion

Several studies have demonstrated successful use of a dynamometer to measure handgrip strength as an indirect assessment of muscle mass in the HD population. A recent study of 330 HD patients found that both muscle strength and muscle mass were strong predictors of mortality, with HGS demonstrating a stronger association with mortality when compared to muscle mass. [32] With similar results found in measurements of HGS taken both before and after HD sessions, this functional test is emerging as a reliable indicator of

muscle mass, although current research is still lacking sufficient data to establish parameters to define muscle wasting. [33; 34; 35]

Body composition measurements, such as bioimpedance analysis (BIA), are frequently used to evaluate fluid balance in the HD population. These devices can also measure several nutritional related markers, such as lean and fat tissue mass [23]. Given the HD population is prone to fluid shifts between intra and extracellular spaces, anthropometric and body composition devices that cannot distinguish between different body compartments of tissue, fat mass and fluid may inaccurately estimate LBM. [36; 37] BIA estimates total body water (TBW) and lean and fat tissue masses by measuring resistance (or impedance) to the flow of an electrical current passed through the body. Hydration status, blood pressure, age and gender can alter the bioelectrical impedance, providing misleading results.[38] Recently, ultrasound techniques that account for fluid shifts are emerging as a useful tool for estimating LBM.[39]

4. Dietary Intake

Unintentional inadequate pro and energy intake is causally linked to PEW. Declines in appetite occur in the early stages of CKD and may be exacerbated by multiple causes such as uremic metabolites and imposed dietary restrictions. [2; 12] As CKD progresses, appetite and intake continue to decline as the dialysis treatment itself can result in physiological and metabolic effects which impact appetite and missed meals during treatment.[40]

Nutritional Assessment Tools

As part of the nutrition care process, assessment of the HD patient includes both a medical history (nutrition intake, biochemical data, medical tests and procedures, anamnesis) and a physical examination (anthropometric measurements, signs of fat and muscle wasting) to determine diagnosis, intervention, monitoring and evaluation. [41; 42] A 2012 survey of 599 Registered Dietitians, 91% of whom worked in the US, revealed that collection of dietary intake is not a standard clinical practice due to time and resource constraints. 70% of dietitians collect intake data only if abnormal laboratory results are found. Two-thirds of dietitians reported analyzing nutrient intake based on estimations without software use.[43] Blood chemistry, such as albumin, serum P, potassium, Kt/V (a measurement of treatment adequacy where K = dialyzer clearance of urea, t = dialysis time, and V = volume of distribution of urea, approximately equal to patient's total body water), lipoproteins, electrolytes, glucose, and nPCR (normalized pro catabolic rate), also known as normalized pro nitrogen appearance (nPNA) provide valuable information of physiological imbalances and nutritional deficiencies. [44] Use of nPNA, which measures net protein degradation, is considered a valid reflection of dietary protein intake (DPI) in steady state conditions. PNA may overestimate DPI during periods of inflammation, be inaccurate for obese, malnourished and edematous patients, and typically underestimates dietary pro intake by approximately 6–8 g of pro per day. [14; 16]

Nutrition focused physical examinations, conducted to detect nutritional deficiencies and complete anthropometric and body composition measurements, though gaining popularity in clinical practice, are still used primarily in research. Several screening tools and scoring systems, such as the subjective global assessment (SGA) and the Geriatric Nutritional Risk

Index (GNRI), and are available to evaluate and monitor changes to nutritional status of the HD patient.[45]

Phosphorus Homeostasis

Phosphorus, the second most abundant mineral in the body, is found in every cell. In an adult, about 85% is complexed with calcium as hydroxyapatite in the bone and 15% is distributed in the intracellular space throughout fluids and soft tissues, with less than 1% found in the plasma. P is not only a structural component of phospholipids (the major component of cell membranes), nucleotides and nucleic acids, but is also involved in several metabolic processes (e.g. is a buffering agent in maintaining pH, stored chemical energy in the form of adenosine tri-phosphate (ATP), and cell signaling through phosphorylation and dephosphorylation).[46]

Physiological process of regulating net phosphate balance

Intestinal Absorption of Phosphate

Ingested P is absorbed both passively and actively through the duodenum, jejunum and ileum of the gastrointestinal tract (GIT) [47]. The primary route of P absorption in the GIT is via passive paracellular diffusion, linearly associated with luminal phosphate concentration, so that a higher dietary intake of P results in increased total amount of absorption. P is also actively transported via sodium-phosphate 2b (NaPi-2b) co-

transporters across the enterocyte. [48; 49] Additionally, calcitriol, or 1,25$(OH)_2$D, stimulates intestinal phosphate absorption by enhancing expression of NaPi-2b co-transporters. [50]

Phosphorus Distribution in the body

Following absorption, inorganic phosphate in the extracellular fluid moves freely in and out of the skeleton, along with calcium, as a consequence of bone remodeling. This critical inorganic phosphate component in the extracellular space makes up less than 0.1 percent of total body P at a concentration of approximately 1 mmol/liter (3.1 mg/dl).[46; 49]

Renal Reabsorption of Phosphorus

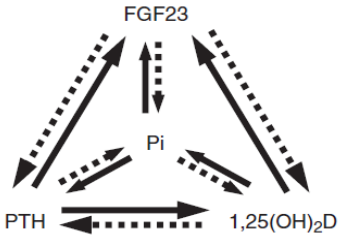
In a healthy kidney, approximately 75% of filtered P is reabsorbed by the glomerulus in the proximal tubule across the hormonally regulated type 2 sodium phosphate co-transporters, NaPi-2a and NaPi-2c. [51; 52] The distal tubule, loop of Henle and collecting duct reclaim the remaining P. The kidneys excrete excess P in the amount of approximately 700-900 mg per day.[49] With diminished functioning of the nephrons in CKD, the kidney lose their ability to excrete excess phosphorus, resulting in hyperphosphatemia.

<u>Hormonal Regulatory Mechanisms of Serum Phosphorus</u>

In order to understand the underlying pathways involved in P homeostasis and the difficulty in managing hyperphosphatemia in CKD, a brief review of the hormonal mechanisms of P homeostasis is provided. As depicted in **Figure 2**, the interplay between fibroblast growth factor-23 (FGF-23), parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D_3

(Calcitriol or $1,25(OH)_2D$) results in a negative feedback loop which regulates P homeostasis.

Figure 2



PTH, $1,25(OH)_2D$ and FGF23 reciprocally regulate their own synthesis and control serum phosphate. In contrast, serum phosphate or phosphate load can regulate production of PTH, $1,25(OH)_2D$ and FGF23. Solid lines indicate stimulation of production or increase in serum level. Broken lines mean inhibition of production or decrease in serum level. PTH and $1,25(OH)_2D$ are also regulated by serum calcium (not shown in the figure).

Reprinted from reference[50]

Fibroblast growth factor-23 (FGF-23)

FGF-23, a hormone synthesized in the osteoclasts, regulates P balance by promoting P excretion and inhibiting vitamin D circulation. A high dietary intake of P stimulates the secretion of FGF-23, which in turn down regulates the expression of the NaPi co-transporters, resulting in phosphaturia. An increase in FGF-23 also limits intestinal P absorption by reducing vitamin D production. FGF-23 inhibits renal 25-hydroxyvitamin D 1-α hydroxylase, the enzyme responsible for the conversion of 25(OH) D to $1,25(OH)_2D$ and also stimulates 24-hydroxlase production, a catabolic pathway for $1,25(OH)_2D$. As nephron capacity diminishes, FGF-23 will rise in a physiological response to maintain serum P levels. Not until the later stages of CKD are elevated serum P levels observed. (53; 54)

Parathyroid hormone (PTH)

Although the primary role of PTH is to regulate serum calcium levels, it has a secondary effect in maintaining P homeostasis. By down regulating NaPi-2a and NaPi-2c in the proximal renal tubule brush border, PTH reduces reabsorption of phosphate in the kidneys. [55] An elevated PTH also increases FGF-23 production, leading to diminished intestinal phosphate absorption and increased renal phosphate excretion. Through a conflicting effect, PTH indirectly enhances intestinal phosphate absorption by increasing the activity of 1-α-hydroxylase enzymes, thus stimulating renal 1,25 D synthesis and also stimulates release of calcium and phosphate from the bone. [56; 57]

1,25-dihydroxyvitamin D_3 (Calcitriol or 1,25(OH)$_2$D)

Vitamin D inhibits phosphate excretion directly repressing PTH and increases intestinal P absorption by up-regulating NaPi-2b expression; however, unlike calcium, vitamin D is not essential for the absorption of P.[58; 59]

To summarize, an elevation in PTH and FGF23 promote phosphaturia by down-regulating sodium-P co-transporters in renal proximal tubule cells. FGF-23 also limits dietary P absorption by reducing 1,25-dihydroxyvitamin D concentrations.

Hyperphosphatemia in Chronic Kidney Disease

Hyperphosphatemia, defined as high serum P levels greater than 1.46 mmol/L,

is common in late stage CKD and is associated with coronary artery calcification (CAC), the development of secondary hyperparathyroidism (SHPT), left ventricular hypertrophy

(LVH), mineral bone disorders (MBD), all-cause and cardiovascular mortality.[60] Atherosclerotic and medial artery calcifications are two types of CAC. Whereas calcification of the intima, or innermost layer of the vasculature, is associated with atherosclerosis resulting from inflammatory mediators and elevated lipids, medial artery calcification is associated with stiffening of the blood vessels associated with age, diabetes, and CKD. Phosphate can stimulate the calcification of vascular smooth muscle cells (VSMCs), which comprise the majority of medial cells. This osteochondrogenic transformation occurs independently of PTH and calcitriol levels.[61; 62] Phosphate has both indirect and direct effects on PTH secretion and the development of secondary hyperparathyroidism in CKD. High dietary P (via increased circulating concentrations of FGF-23) lowers calcitriol levels, thus stimulating PTH. [61] Chronic hyperphosphatemia in CKD leads to hyperplasia of the parathyroid glands, resulting in elevated PTH levels [63] This increase in PTH stimulates release of P from the bone, leading to CAC. Both dietary phosphate and PTH increase FGF-23 levels. Consequences of prolonged exposure to FGF-23 in CKD include increased prevalence LVH, resulting from direct inducement of cardiomyocyte hypertrophy via the phospholipase C (PLC) γ/calcineurin/nuclear factor of activated T-cells (NFAT) pathway. This cardiovascular complication affects approximately 75% of patients beginning RRT. [64]

Sudden death, arrhythmia, and unknown were the most common causes of cardiac death reported in the USRDS and Hemodialysis (HEMO) study. LVH, cardiac fibrosis, and electrolyte anomalies may have been the underlying factor in these CVD deaths. [21] Numerous studies have found an association between elevated serum P and an increased

risk in cardiovascular morbidity and mortality in ESRD patients, which may be attributed to the presence of CAC and accelerated atherosclerosis. [65]

Phosphate levels are central to chronic kidney disease-mineral and bone disorder (CKD-MBD), a syndrome that defines the mineral, hormonal, bone remodeling anomalies, and vascular and soft tissue calcification that occur in CKD. Abnormalities in calcium, P, FGF 23, PTH, and vitamin D metabolism lead to CKD-MBD and are associated with increased morbidity and mortality. [66]

Phosphate control in dialysis

Removal of phosphate during the dialysis procedure differs from urea or other small molecules. Water molecules bind to P, converting what was originally a small molecule into one of medium size, making passage through dialysis pores more difficult. Transfer rate of phosphate from intra to extracellular compartments additionally limits removal during dialysis. Slow shifts from the intracellular, or inaccessible space, to the extracellular compartment and accessible plasma pose a barrier to phosphate removal. As a result, serum P levels drop quickly during the first hour of dialysis, and then stabilize; therefore, longer dialysis sessions result in greater P removal. With dietary P intakes of 0.8 to 2.0 grams per day, the average P removal of 800–1200 mg/session does not remove enough P. Use of phosphate binders is commonplace as an adjunct therapy to both dietary restriction and P removal from dialysis; however, these complementary measures of P control should not downplay the importance of dietary P restriction. Within a healthy population, a high dietary P intake, even in the absence of elevated serum P, is associated with increased

mortality.[67] A drop in serum P levels as a result of reduced dietary P intake and P binders use has been shown.[60; 68; 69] However, relying on measures of serum P to gauge dietary control of this mineral has been criticized as unreliable due to inaccurate measurement techniques, frequency and timing of serum samples, and tendency with daily fluctuations in serum levels, potentially providing false assurance that P intake is controlled. Alternative biomarkers, such as FGF-23 and PTH have been suggested as better measures of cumulative P burden. [70; 71]

Metabolic Acidosis

Metabolic acidosis is a CKD induced complication as a result of reduced hydrogen ion excretion, primarily from the metabolism of sulfur containing amino acids. Although buffers, such as bicarbonate, are added to the dialysate to correct the acidosis, many patients remain acidotic. Metabolic acidosis stimulates net pro catabolism, increases oxidation of branched chain amino acids (BCAA), suppresses albumin synthesis, negatively impacts bone metabolism, and impairs glucose tolerance. [72] Correction of acidosis may reduce pro wasting and restore BCAA muscle pro concentration; however, treatment of acidosis may only improve impaired pro synthesis in the absence of inflammation. [73; 74]

Diets that produce large acid loads from the consumption of excess nucleic and amino acids in meats coupled with inadequate intakes of organic bases from fruits and vegetables may not only lead to low normal plasma bicarbonate concentrations, but also may impair calcium and pro metabolism. [75]

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

CKD-MBD, a term originating from the Kidney Disease Improving Global Outcomes (KDIGO) group, describes the complex of mineral and skeletal disorders and vascular and soft tissue calcification resulting from abnormalities of calcium, P, PTH, or vitamin D metabolism caused by CKD. Mineral bone disorders are among the non-traditional risk factors which contribute to the high rate of cardiovascular morbidity and mortality observed in CKD. [76] Efforts to control one factor can negatively impact remaining factors. For example, vitamin D supplements, often prescribed to HD patients, can increase the risk of hyperphosphatemia through increased GIT absorption of phosphate as well as stimulation of bone resorption. [77; 78; 79]

Dietary Phosphate

Challenges in menu planning and dietary adherence exist for the HD population as they are instructed to restrict dietary P while increasing protein to 1.2 grams per kg body weight, with an emphasis of at least 50% of protein coming from foods of high biological value (animal based foods).[31] Instruction presented to patients with hyperphosphatemia in limiting dietary P, usually provided as a list of high P foods to avoid, may have the unintended consequence of a reduced protein intake. Currently, HD patients are counseled to reduce intake of dietary P by limiting or restricting foods high in P, including meat, poultry, fish, dairy, beans, lentils, and nuts. This educational practice may explain why improved survival among HD patients with prescribed dietary P restriction has not been found.[80] Additional dietary restrictions for sodium, potassium and fluid make meal

planning and dietary adherence burdensome. Dietary protein intake for most dialysis patients reported at < 1.0 gram per kg/day is inadequate to preserve muscle. A diminished pro intake as a result of limiting dietary P may lead to PEW. Both low dietary pro intakes, elevated dietary P intakes and elevated ratios of dietary P/pro intakes have been associated with increased mortality in MHD patients.[1; 81] Ideally, HD patients would benefit from a diet which is both high in pro and low in bioavailable P. Using a ratio of milligrams of P per gram of pro, or P/pro ratio, to identify foods which are both high in pro and low in P has been suggested as a potential strategy in meal planning. Taking into account loss of P through various cooking methods, P bioavailability, and pro to P ratios, D'Alessandro, et. al has proposed a phosphorus pyramid tool (see **Figure 3**) as a guide to choosing foods both high in protein and low in bioavailable P. Authors of the pyramid suggested an upper limit of 12 mg/g to identify foods with a favorable phosphorus to protein ratio[82], a level in agreement with The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI**)** guidelines of a recommended a daily P intake of 10 to 12 mg/g of protein.[83] Animal proteins vary in their phosphorus and protein content. A whole egg contains 6 g of protein and 86 mg of phosphorus, whereas the egg white contains 3.6 g protein and only 5 mg of phosphorus, a P/pro ration of less than 2 mg/gram.[84]

Figure 3

Phosphorus Pyramid

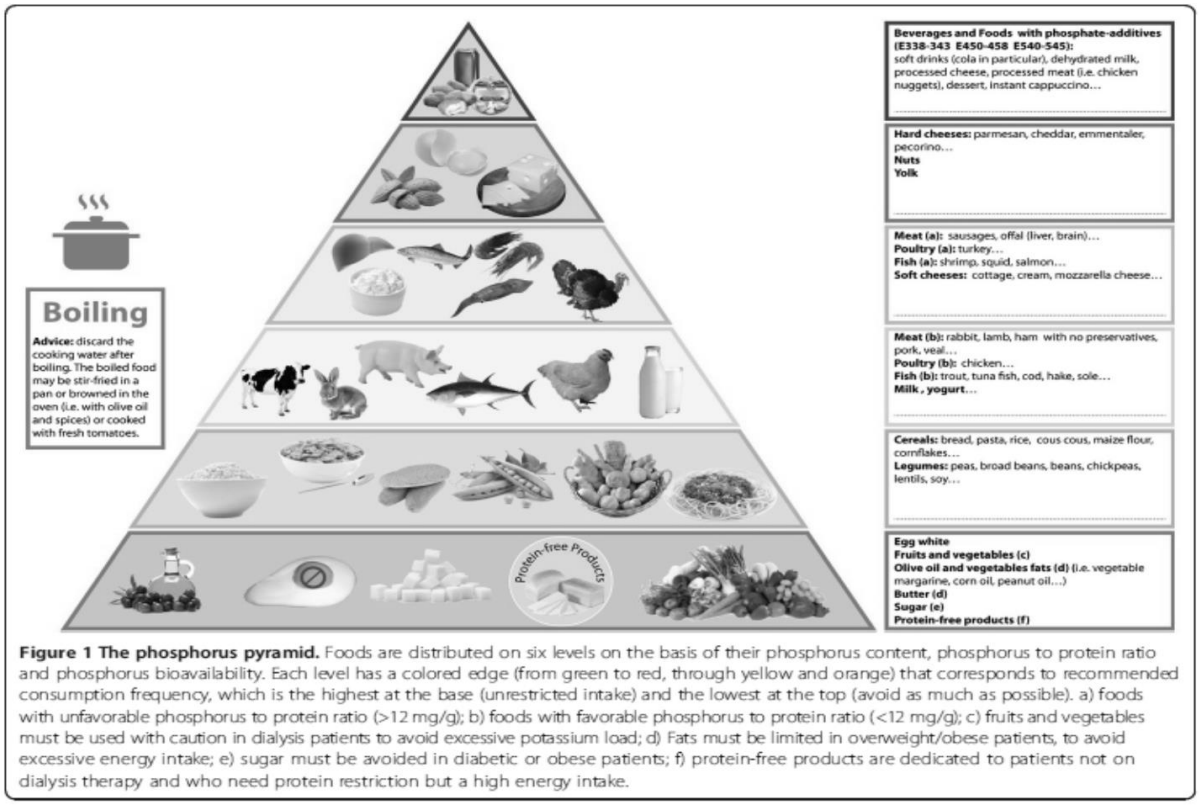


Figure 1 The phosphorus pyramid. Foods are distributed on six levels on the basis of their phosphorus content, phosphorus to protein ratio and phosphorus bioavailability. Each level has a colored edge (from green to red, through yellow and orange) that corresponds to recommended consumption frequency, which is the highest at the base (unrestricted intake) and the lowest at the top (avoid as much as possible). a) foods with unfavorable phosphorus to protein ratio (>12 mg/g); b) foods with favorable phosphorus to protein ratio (<12 mg/g); c) fruits and vegetables must be used with caution in dialysis patients to avoid excessive potassium load; d) Fats must be limited in overweight/obese patients, to avoid excessive energy intake; e) sugar must be avoided in diabetic or obese patients; f) protein-free products are dedicated to patients not on dialysis therapy and who need protein restriction but a high energy intake.

reprinted from reference[82]

About 40 to 60% of organic P, found in animal based foods and plants, is absorbed, whereas the bioavailability of inorganic P, found in processed foods, is almost 100%. Given humans do not express the enzyme phytase, which is required to hydrolyze phytic acid or phytate, the storage form of P found in plants, the P content of plant pro may not reflect actual absorption.[84] Yet, this diminished bioavailability of phosphorus from vegetarian sources of protein is not considered in renal menu planning, nor reflected in nutrient data bases.

Phosphorus additives, used by the food industry as acidity regulators, preservatives, thickeners, emulsifiers, flavor enhancers and stabilizers, may contribute as much as 1000 mg/d of phosphorus to the diet.[85; 86] A recent 2010 survey of almost 2400 processed grocery items revealed that 44% contained added P.[87] Currently, the United States Department of Agriculture (USDA) food composition data base lists total amount of P per serving, but does not distinguish between inorganic and organic P content. Additionally, the P content listed in nutrient databases does not always reflect the actual P content, and has been shown to underestimate P by as much as two to three fold. [88] Both the USDA and the Ministry of Health in Malaysia require that manufacturers label for the presence of phosphates or polyphosphates on food labels; however, P amount is not a requirement for the nutrient fact panel. Because the amount of P is not listed as a nutrient on food labels, HD patients must be educated in identifying inorganic P additives, such as "monosodium phosphate", "phosphoric acid", and "sodium hexametaphosphate", on ingredients labels. Despite food labeling laws, an independent analysis of food labels of enhanced uncooked meat and poultry products found that manufacturers do not always disclose additives ingredients, making it impossible to estimate phosphorus and potassium content.[89] Fast foods, processed meats such as ham and sausage, processed cheeses, canned fish, baked goods and cola type beverages, typically contain large amounts of added phosphate.[90]

Additionally, various cooking methods have been evaluated to measure their effect on P content. Boiling sliced meats in soft water or use of a pressure cooker has been shown to reduce P content as much as fifty percent while preserving pro content.[91] Phosphorus

content of pasta, rice, fresh and frozen vegetables can be reduced from 7% up to 43% by soaking and boiling methods.[92]

Phosphate Binders

In conjunction with limiting dietary P, both prescription and non-prescription phosphate binders are taken with meals to reduce P absorption in the gastrointestinal tract. Binders are generally classified as calcium based and non-calcium based, with the most commonly prescribed binders reported as calcium-based agents despite known associations with cardiovascular calcification. Calcium based binders, such as calcium carbonate and calcium acetate, are inexpensive, tolerated well, and can lower parathyroid levels, factors most likely related to their continued widespread use. In patients with elevated serum calcium levels, known CAC or low serum PTH levels, calcium based binders are contraindicated. Two non-calcium based binders, sevelamer and lanthanum, are both associated with increased gastrointestinal side effects and sevelamer binds with bile salts, reducing lipid levels and potentially interfering with the absorption of fat soluble vitamins. Among all chronic disease categories, the HD population has one of the highest pill burdens. Results from a cross-sectional study of 233 prevalent US dialysis patients found that from an average burden of eleven pills, 49% were phosphate binders with a 70% patient adherence rate.[93; 94]

P absorption in the intestine is dependent upon the amount dietary P, bioavailability, use of P binders, and presence of 1,25(OH)2 vitamin D. Additional barriers to controlling P may be related to patient education. Erroneous beliefs that phosphate restriction is not

necessary with binder use, poor adherence to binder use, unknown associations between hyperphosphatemia and CAC, and confusion in which foods are high in P may all be associated with hyperphosphatemia.[95]

The dialysis diet contradicts a healthy eating pattern. Difficulty in planning and implementing dietary restrictions often results in inadequate nutrient intakes. Whole grains, pulses, nuts, fruits and vegetables are typically restricted in the renal diet due to their higher content of potassium and P, yet intake of these foods are associated with reduced CVD and overall mortality.[96; 97; 98]

Dietary P intake can be reduced without compromising pro consumption by choosing foods with P/pro ratios less than 12 mg/g, avoiding foods with phosphate additives, and employing cooking techniques which lower the P content.[82; 99]

Poor outcomes related to both hyperphosphatemia and PEW within the HD population have been well documented; however, to our knowledge, there have been no published studies examining intakes of P/pro ratios and PEW relationships in Malaysian HD patients.

CHAPTER III: Methodology

Study Design and Patient Recruitment

This cross sectional study was part of a baseline screening protocol for an interventional Vitamin E tocotrienol clinical trial entitled PATCH (Palm Tocotrienols in Chronic Hemodialysis) to evaluate treatment effects on lipoprotein panels and inflammatory biomarkers. Patients were recruited from two dialysis non-governmental organization, or

NGO, (National Kidney Foundation) clinics and two government hospitals in the Klang Valley, Malaysia, between October 2015 through March 2016.

A sample of sixty MHD patients taken from four clinics (15 patients per clinic) were chosen from a larger screening pool (40 patients per clinic) based on the completion of data recorded.

Inclusion criteria for the study included patients aged 18-70 years, willing to provide informed consent, receiving thrice weekly HD treatment for at least three months. Exclusion criteria included poor adherence to prescribed medication and HD regimen and impaired cognitive and functional abilities. This study (Nutritional Status and Lifestyle Assessment among HD Patients in Malaysia) was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (NMRR-15-865-25260) and Medical Research Ethics Committee of National University of Malaysia (NN-039-2015).

Demographic and medication data collection

Demographic and prescription medication information obtained from the medical chart was reviewed with the patient for accuracy.

Anthropometric and body composition measurements

Pre and post dialysis weights were taken using a SECA digital scale (Model 220, SECA, Germany) and height was measured using a stadiometer to derive BMI (kg/m^2). Triceps skinfold thickness (TSF) measurement was taken on the non-fistula arm using a Harpenden skinfold caliper (HSK-BI, British Indicators, West Sussex, UK). Mid-upper arm circumference (MAC) was measured using a non-stretch Lufkin® metal measuring tape

(Apex Tool Group, LLC, NC, USA). International Society for the Advancement of Kinanthropometry (ISAK) techniques were employed in the measurements for MAC and TSF[100]. MAMC and MAMA measurements were derived using the formulas listed in **Table 3**. Hand grip strength (HGS) was measured using a Jamar dynamometer (BK-7498; Fred Sammons, Inc., Burr Ridge, IL) on the non-fistula hand prior to the patient's dialysis session. Three measurements were taken in the standing position, and the mean value was used in all statistical analyses. All anthropometric measurements were performed by an International Society for the Advancement of Kinanthropometry (ISAK) trained dietitian to eliminate inter-observer variation. Prior to the HD session, body composition measurements were completed using a portable bio-impedance spectroscopy monitor (Body Composition Monitor, Fresenius Medical Care, Bad Homburg, Germany). The body composition monitor (BCM) used body weight, height, and measurements of whole body intracellular water (ICW) and extracellular water (ECW) using bioimpedance spectroscopy to determine lean tissue mass (LTM), adipose tissue mass (ATM) and overhydration (OH).[101]

Biochemical analysis

Serum samples for routine renal biochemistry (serum albumin, potassium, P, hsCRP, and lipid profiles) were analyzed using standard automated laboratory techniques by an external laboratory (Roche/Hitachi 912 System, Roche Diagnostics, Tokyo, Japan).

3-day dietary recall collection and analysis

Per KDOQI guidelines, 3-day dietary recalls, including two non-dialysis and one dialysis day, were collected by trained dietitians using household measures to estimate portion sizes.[102] Nutrient analysis of the diet records were analyzed using the Nutritionist Pro software (Nutritionist Pro™ 2.2.16, First DataBank Inc., 2004). Dietary energy intake (DEI) and dietary pro intakes (DPI) were calculated based on the patient's dry weight.

QOL (Quality of Life)

The Kidney Disease Quality of Life-36 (KDQOL-36) survey, a kidney disease-specific measure of health-related quality of life (HRQOL), was administered by a trained dietitian. The survey contains questions related to generic chronic disease as well 24 kidney disease specific questions. A scoring instrument was used to summarize the questions into four scores: effects of kidney disease, burden of kidney disease, SF-12 physical composite, and SF-12 mental composite [SF-12 refers to the generic core derived from the Medical Outcomes Study Short Form 36 (MOS SF-36), which measures eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health]. Scores ranged from 0%, equivalent to maximum disability, to 100%, equivalent to zero disability.[103]

PEW assessment

Patients satisfying PEW criteria per the ISRMN were identified, and PEW prevalence was assessed. Serum chemistry, BMI, muscle mass, and dietary intake parameters used included albumin < 3.8 mg/dL, BMI < 23 kg/m^2, MAMC below the 10th percentile of the

normal population from the NHANES I study, and a dietary energy intake of < 25 kcals/kg body weight, respectively.[31; 104]

Statistical analysis

Variables are presented as mean ± SD, or frequency (percentages). The normal distribution for continuous variables was assessed using Kolmogorov-Smirnov (K-S) test. Comparisons were performed by the Student's-t and Mann-Whitney tests for continuous variables, with and without normal distribution, respectively. Comparisons of frequencies were carried out by the Fisher test. Differences between groups were analyzed using one-way ANOVA and Kruskal-Wallis H Tests, with and without normal distribution, respectively. Linear relationships for continuous variables were evaluated using Pearson's correlation. Categorical variables were evaluated for association using Pearson's Chi-Square test. Statistical analyses were carried out using SPSS version 23 (IBM, Chicago, IL, USA). Statistical significance was set at $P < 0.05$ for all evaluated parameters. A non-significant p value of $0.05 < p \leq 0.10$ was used for discussion purposes.

CHAPTER IV: RESULTS

Patient Characteristics

Table 4 outlines the demographics of the sample (n=60) HD population. Almost half of the patient population was Chinese, over one-third Malay, and over one-eighth Indian. Males and females were equally distributed among the sample population. Over two-thirds of the group had at least a secondary education and over two-thirds were unemployed.

Table 4 Demographic characteristics of the study population

Demographics (n=60**)**	
Age (years)	55.1 ± 13.3
Ethnicity (%)	
Chinese	29 (48.3%)
Malay	21 (35%)
Indian	9 (15%)
Others	1 (1.7%)
Sex	
Males (%)	32 (53.3%)
Females (%)	28 (46.7%)
Marital Status (%)	
Married	48 (80%)
Single	12 (20%)
Education	
None	4 (6.7%)
Primary	15 (25%)
Secondary	28 (46.7%)
College/University	13 (21.7%)
Employed	
Yes	17 (28.3%)
No	43 (71.7%)

Data are expressed as mean ± SD or percentage

Anthropometric and body composition measurements were compared between genders as outlined in **Table 5**. As anticipated, both mean and highest HGS measurements, lean tissue mass, height, and MAC was found to be significantly higher for males when compared to females.

Table 5 Anthropometric and Body Composition Measurements

	ALL (n=60)	**Men (n= 32)**	**Women (n=28)**	***P* for comparison between genders**
Age (y)	55.1 ± 13.3	55.4 ± 14.5	54.8 ±12.0	0.609
Time on dialysis (mo)	90.9 ± 70.8	98.1 ± 73.9	82.9 ± 67.5	0.366
Body weight (kg)	62.9 ± 18.8	64.8 ± 23.3	60.7 ± 11.7	0.534
Stature (cm)	156.7 ± 7.8	160.8 ± 6.6	152.0 ± 6.2	**<0.0005**
BMI (kg/m^2)	25.4 ± 6.3	24.8 ± 7.3	26.1 ± 5.0	0.103
MAC (cm)	30.1 ± 6.3	29.0 ± 6.7	31.3 ± 5.7	**0.017**
TSF(mm)	18.7 ± 8.9	15.0 ± 6.1	23.0 ± 9.7	**0.001**
MAMC (cm)	24.2 ± 5.1	24.3 ± 5.4	24.1 ± 4.8	0.801
MAMA (cm^2)	48.0 ± 22.1	48.5 ± 26.2	47.5 ± 16.7	0.722
Lean Tissue mass (kg)	32.8 ± 10.9	38.1 ± 11.9	26.8 ± 5.0	**<0.0005**
Fat Tissue Mass (kg)	21.7 ± 10.4	19.4 ± 11.5	24.4 ± 8.4	0.002
HGS – mean (kg)	18.6 ± 6.1	21.7 ± 6.4	15.1 ± 3.2	**<0.0005**
HGS – highest (kg)	19.8 ± 6.3	22.9 ± 6.7	16.4 ± 3.3	**<0.0005**

BMI: body mass index; MAC: mid-arm circumference; TSF: triceps skin fold; MAMC: mid-arm muscle circumference; MAMA: mid-arm muscle area; HGS: hand grip strength
Data are expressed as mean ± SD; Mann-Whitney U Test
Statistically significant variables are given in bold

Average intakes from the three-day diet recall for HD nutrients of concern were evaluated against KDOQI guidelines and between genders as demonstrated on **Table 6**. As expected, overall intake for males was higher than that for females. Intakes for P, sodium, and fluid fell within KDOQI guidelines; however, neither males nor females met calorie goals of 30 to 35 kcals per kg or pro goals of 1.2 grams per kg body weight.[31]

Table 6 Nutrient Intake Analysis of 3 Day Diet Recall

Nutrient Intake Analysis					
	All	Men (n= 32)	Women (n=28)	*P* for comparison between genders	NKF KDOQI guidelines[31]
Energy (kcals)	1445 ± 393	1512 ± 454	1370 ± 299	0.163	Based on BW
Pro (g)	54 ± 18	57 ± 19	50 ± 18	0.197	Based on BW
Potassium (mg)	990 ± 403	1049 ±449	923 ± 340	0.229	Based on serum levels
Sodium (mg)	2511 ± 1583	2419 ± 1226	2060 ± 910	0.219	<2400 mg
P (mg)	618 ± 214	667 ± 227	563 ± 189	0.062	10-17 mg/kg/day (~630-1071)
Fluid (ml)	1002 ± 325	1064 ± 331	932 ± 309	0.118	750-1500 cc/day
DEI (kcals/kg dry wt.)	24.0 ± 7.7	24.4 ± 7.8	23.6 ± 7.8	0.709	30-35 kcals/kg
DPI (gms pro/kg dry wt)	0.90 ± 0.38	0.9 ± 0.35	0.9 ± 0.41	0.704	1.2 gms/kg aBWef^

^edema-free adjusted body weight
Data are expressed as mean ± SD as analyzed by Student's t-test

P/pro Ratio

Average ratio of P/pro intake for the entire sample population was 11.9 mg/g ± 3.2. P/pro ratio was further stratified into favorable (< 12 mg/g) and unfavorable (> 12 mg/g) groups of P/Phos intakes (**see Table 7**)[82]. Average ratios of P/pro intake of the favorable and unfavorable group were 9.8 ± 1.6 and 15 ± 2.3, respectively. Differences in various biochemical, anthropometric and dietary intakes between the favorable and unfavorable groups were analyzed. P/pro ratio, serum potassium, dietary P, dietary pro, and KDQOL

SF-12 physical composite scores were significantly improved with favorable P/pro intakes when compared to unfavorable intakes. Favorable P/pro intakes were also associated with higher intakes of protein per kg of body weight, lower total serum cholesterol and reduced inflammation, as measured by hsCRP.

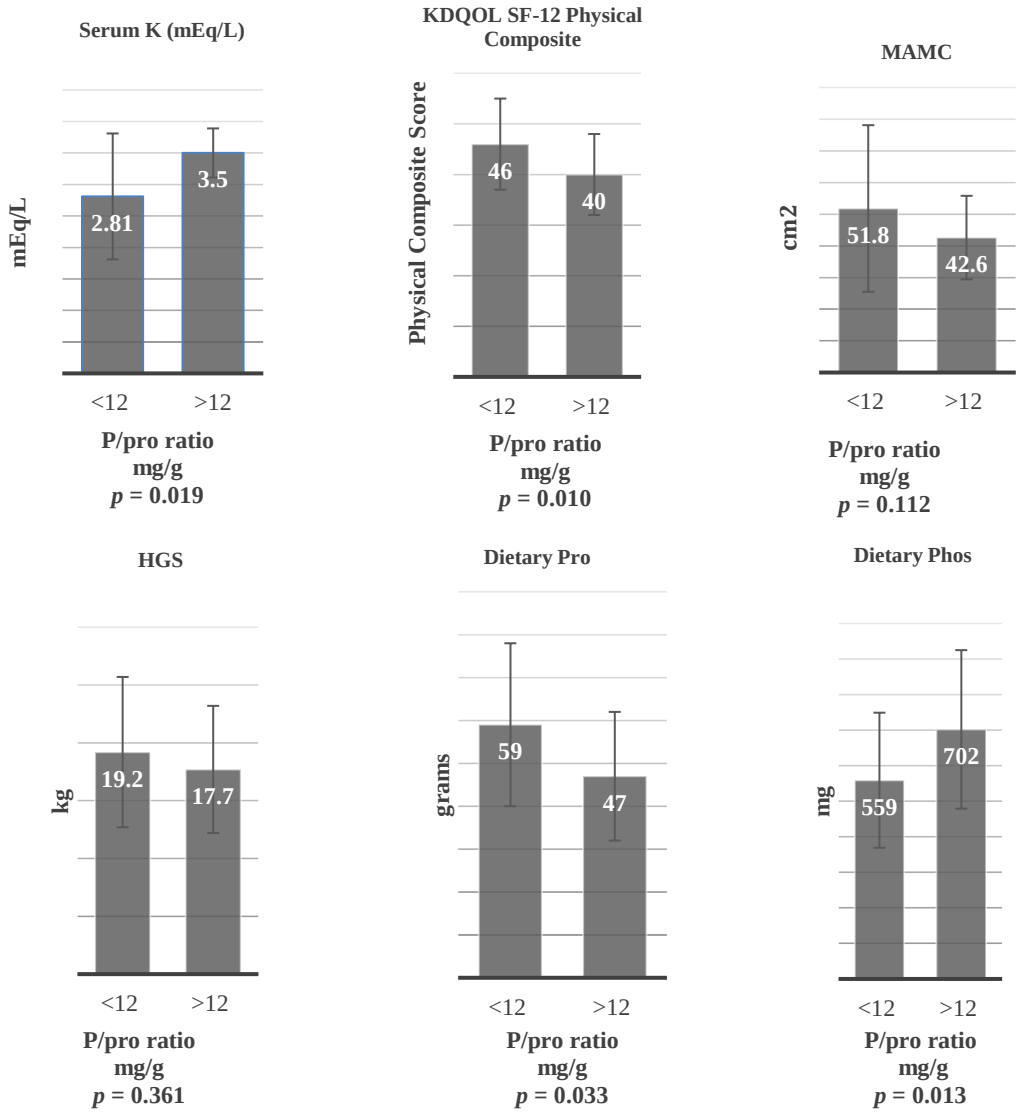
Table 7 Relationship of P/pro ratio (<12 mg/gram and >12 mg/gram) and biochemical, anthropometric and dietary intake

	P/pro ratio <12 mg/gram (n=35)	**P/pro ratio > 12 mg/gram (n=25)**	***P* value**
P/pro ratio (mg/gram)	9.8 ± 1.6	15 ± 2.3	**<0.0005**
Serum Phos (mg/dL)	5.36 ± 1.3	5.39 ± 1.7	0.921
Serum K (mEq/L)	2.81 ± 1.0 (n=10)	3.5 ± 0.39 (n=12)	**0.019**
Serum alb (g/dL)	3.96 ± 0.36	3.84 ± 0.34	0.204
Total cholesterol (mg/dL)	162 ± 32	179 ± 48	0.100
Lean tissue mass	33.5 ± 11.5	32.3 ± 10.2	0.762
Fat tissue mass	22.0 ± 11.6	21.3 ± 8.7	0.781
ECFv/TBW	1.97 ± 0.45	1.78 ± 0.34	0.111
BMI (kg/m^2)	25.8 ± 7.2	25.9 ± 4.9	0.601
hsCRP (mg/L)	5.00 ± 4.9	7.6 ± 7.5	0.105
Dietary Phos (mg)	559 ± 190	702 ± 223	**0.013**
Dietary Pro (g)	59 ±19	47 ± 15	**0.033**
DPI (grams/kg)	0.97 ± 0.4	0.80 ± 0.3	0.086
DEI (kcals/kg)	24.1 ± 7.6	24.0 ± 8.3	0.956
KDQOL SF-12 Physical Composite	46 ± 9	40 ± 8	**0.010**
MAMC (cm)	25.1 ± 5.5	23.0 ± 4.2	0.112
MAMA (cm^2)	51.8 ± 26.3	42.6 ± 13.2	0.114
Mean HGS (kg)	19.2 ± 6.5	17.7 ± 5.5	0.361

Phos: P; K: Potassium; alb: albumin; ECF: extra cellular fluid: TBW: total body water; hsCRP: high sensitivity C-reactive pro; DPI: dietary pro intake; DEI: dietary energy intake; KDQOL: Kidney Disease Quality of Life
Data are presented as mean ± SD; statistical significance measured by Kruskal-Wallis H Test
Statistically significant variables are given in bold

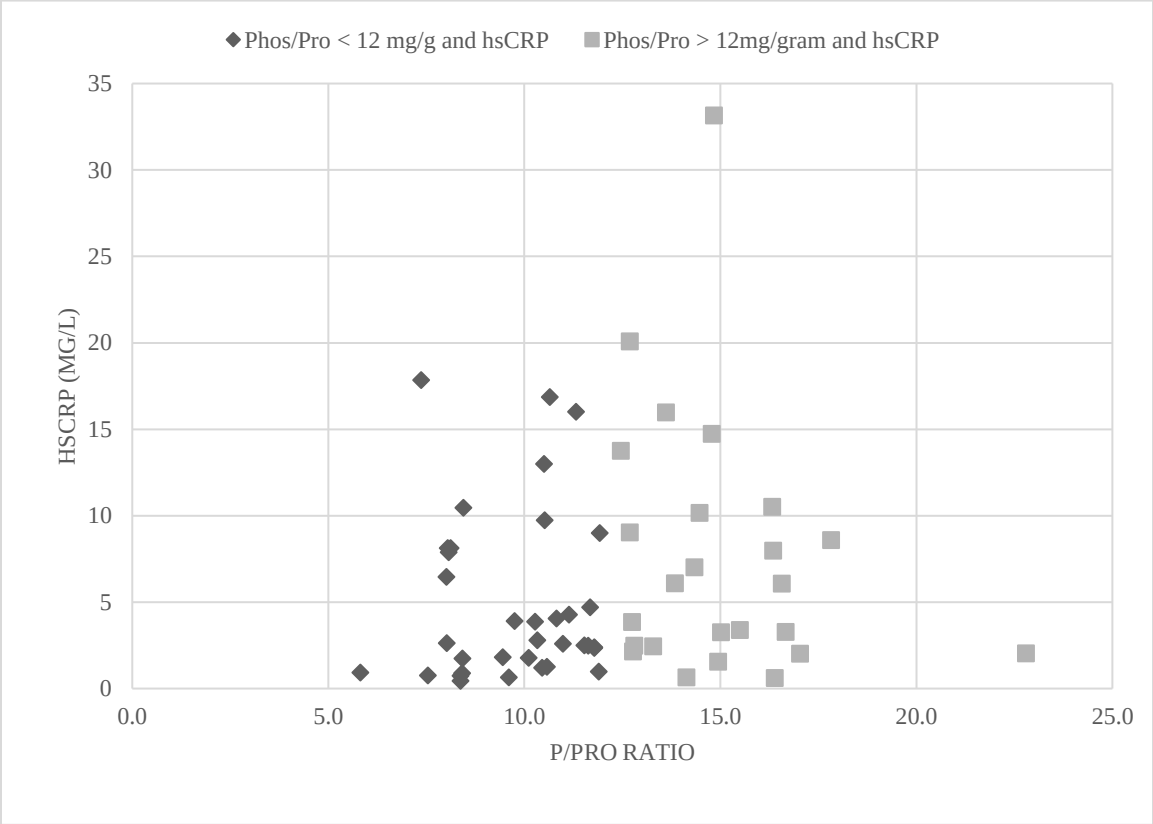
As illustrated in **Figure 4**, favorable P/pro intakes were associated with a lower serum potassium (K), hsCRP, improved KDQOL SF-12 physical composite scores, higher HGS, and MAMC. The favorable ratio is influenced equally by P and pro intakes.

Figure 4 Relationship of P/pro Ratios and various clinical indicators



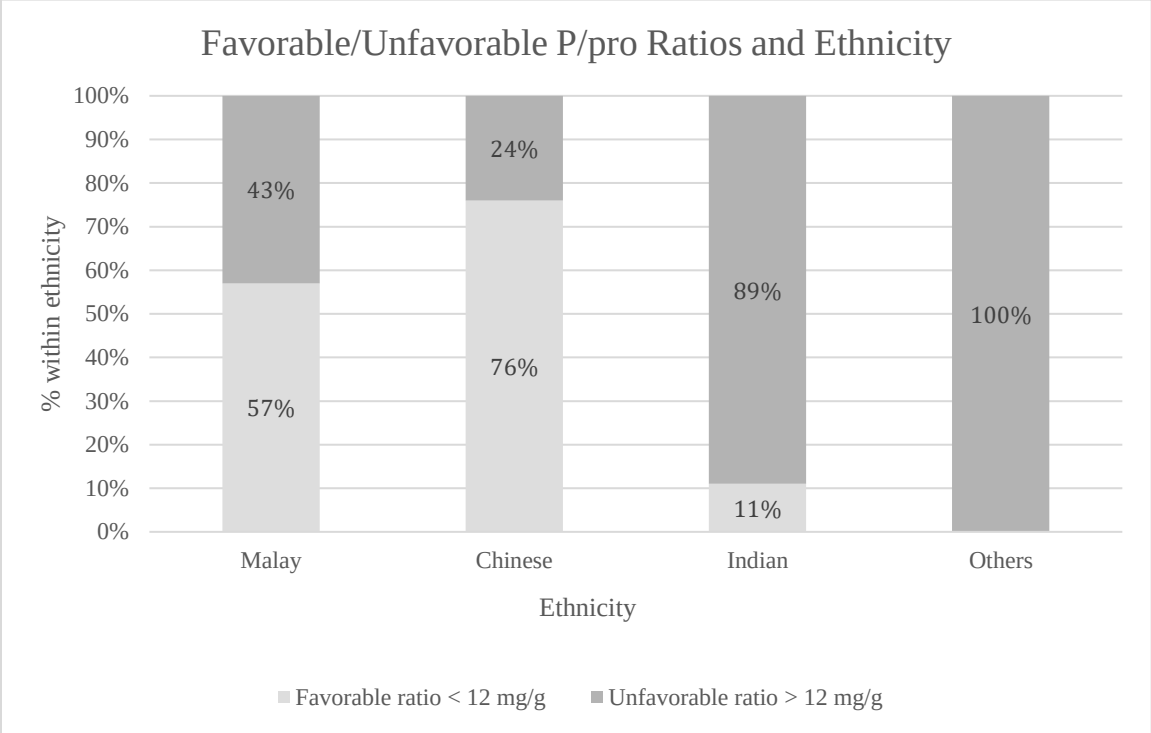
The mean hsCRP in the favorable and unfavorable P/pro groups were 5.0 ± 4.9 and 7.6 ± 7.5 (p = 0.105), respectively, as depicted in **Figure 5**. Although not significant, these differences reflect a trend towards increased inflammation with higher P/pro ratio intakes.

Figure 5 Relationship of P/Pro Ratio (< 12 mg/gram and > 12 mg/gram) and hsCRP



Within each ethnic group, 76% of Chinese and 57% of Malay patients had P/pro intakes in the favorable range (< 12 mg/g) in comparison to 11% of Indian patients, as illustrated in **Figure 6**.

Figure 6 Comparison of P/pro Ratios and Ethnicity

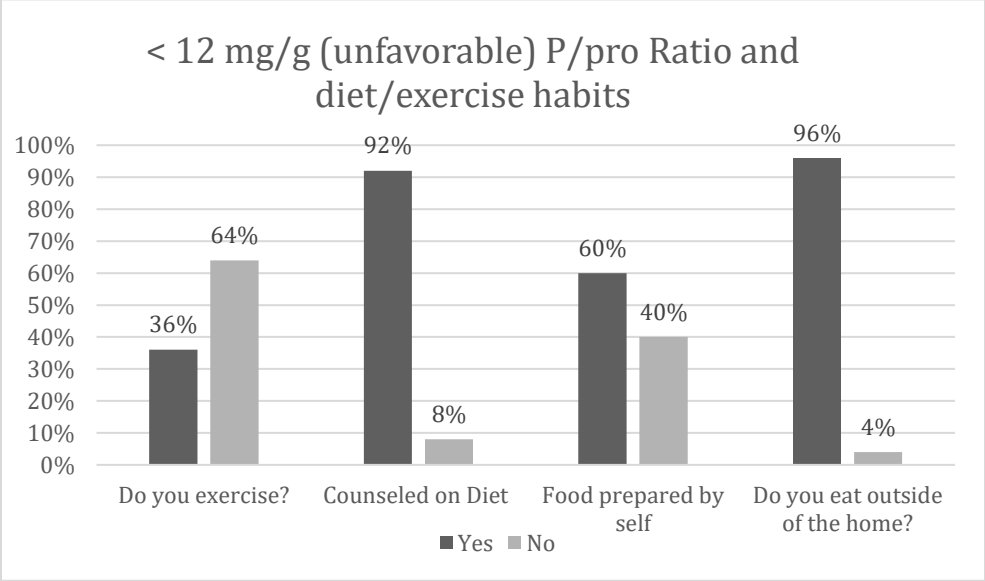


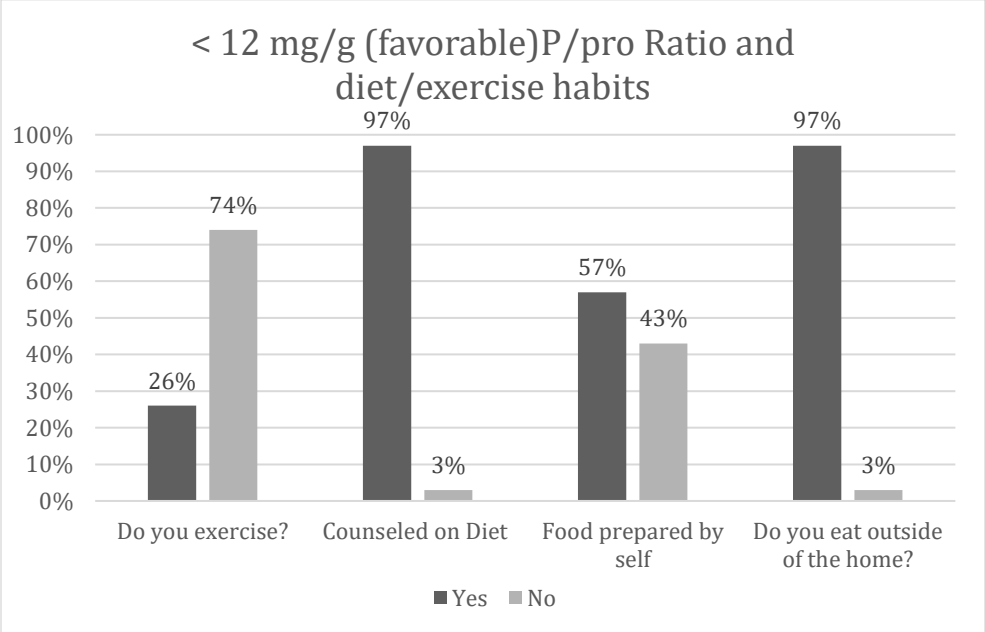
Pearson's Chi-Square (*p* value = 0.004)

In comparing diet and exercise habits between favorable and unfavorable P/pro intakes, those patients consuming unfavorable ratios were 44% less likely to exercise in comparison to those consuming favorable ratios, who were 65% more likely to exercise. Both groups reported similar dietary habits regarding food preparation, food consumption outside of the home, and dietary counseling (see **Figure 7**).

Figure 7

Comparison of P/pro ratios and diet/exercise habits



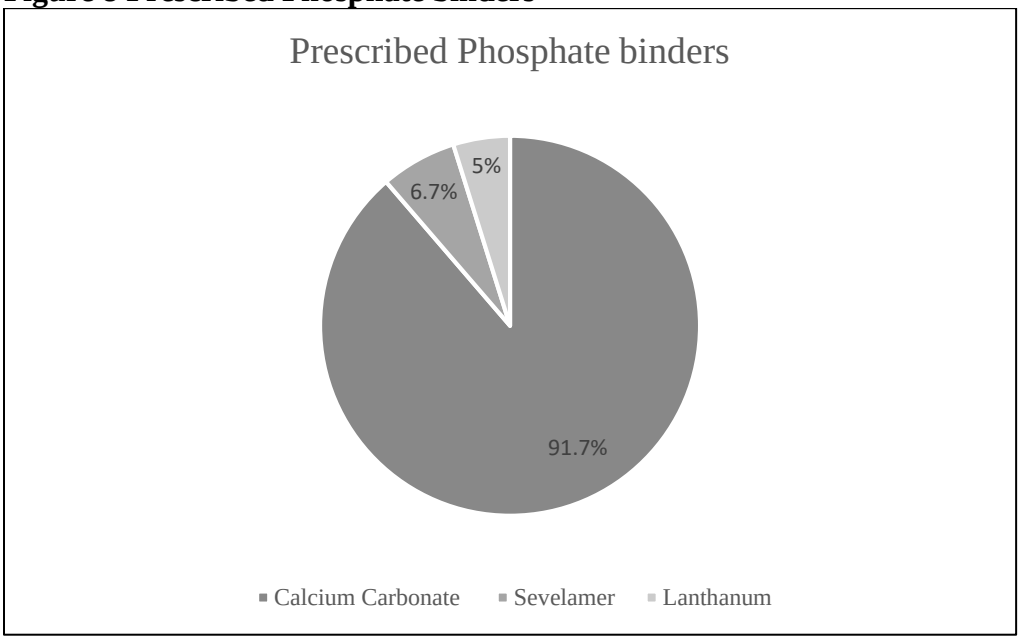


Fisher's Exact Test Chi-Square

Phosphate Binders

Among the phosphate binders prescribed to this Malaysian population, 91.7% take calcium carbonate, with less than 12% using non-calcium based binders as depicted in **Figure 8**.

Figure 8 Prescribed Phosphate binders



Frequency Pie Chart

Measures of Muscle Mass

As illustrated in **Table 8**, in comparing various measures of muscle mass, MAMC and MAMA were significantly correlated with measurements of lean tissue mass, fat tissue mass and BMI. Mean HGS was significantly correlated with MAMA, and lean tissue mass.

Table 8 Matrix of Pearson's correlation coefficients among HGS, anthropometric, and body composition variables

Variable	BMI	MAMC	MAMA	Lean Tissue mass	Fat tissue mass
BMI (kg/m^2)					
MAMC (cm)	0.752**				
MAMA (cm^2)	0.815**	0.962**			
Lean tissue mass	0.448**	0.447**	0.517**		
Fat tissue mass	0.878**	0.637**	0.710**	0.123	
Mean HGS (kg)	0.167	0.238	0.255*	0.645**	0.014

P < 0.01** n= 60 (32 men and 28 women)
P < 0.05*

Anthropometric, body composition and biochemical measurements of those HD patients who answered "yes" when asked if they engaged in any form of exercise were compared to those patents who reported no physical activity (see **Table 9**). Those who exercised had a significantly lower BMI (22.3 ± 3.8) than non-exercisers (26.7 ± 6.7). Exercisers also had a significantly lower fat tissue mass (16.8 ± 5.6) and MAMC (21.7 ± 5.3) than non-exercisers (23.8 ±11.3, 25.3 ± 4.7, respectively). Although not significant, those who reported exercising showed trends towards higher serum HDL, serum albumin and lower hsCRP levels.

Table 9 Anthropometric, Body Composition and Biochemical Measurements of exercisers vs non-exercisers

Do you exercise?	**Yes (n=18)**	**No (n= 42)**	**P value**
BMI (kg/m^2)	22.3 ± 3.8	26.7 ± 6.7	**0.012**
Mean HGS (kg)	19 ± 6.4	18 ± 6.1	0.741
Serum HDL (mg/dL)	43 ± 14	41 ± 11	0.528
Serum hsCRP (mg/L)	4.6 ± 5.4	6.7 ± 6.4	0.216
Serum alb (mg/dL)	4.0 ± 2.4	3.9 ± 3.9	0.219
Lean tissue mass	32.5 ± 8.9	32.9 ± 11.7	0.880
Fat tissue mass	16.8 ± 5.6	23.8 ±11.3	**0.017**
MAMC (cm)	21.7 ± 5.3	25.3 ± 4.7	**0.011**

Data are expressed as mean ± SD as analyzed by one-way ANOVA
Statistically significant variables are given in bold

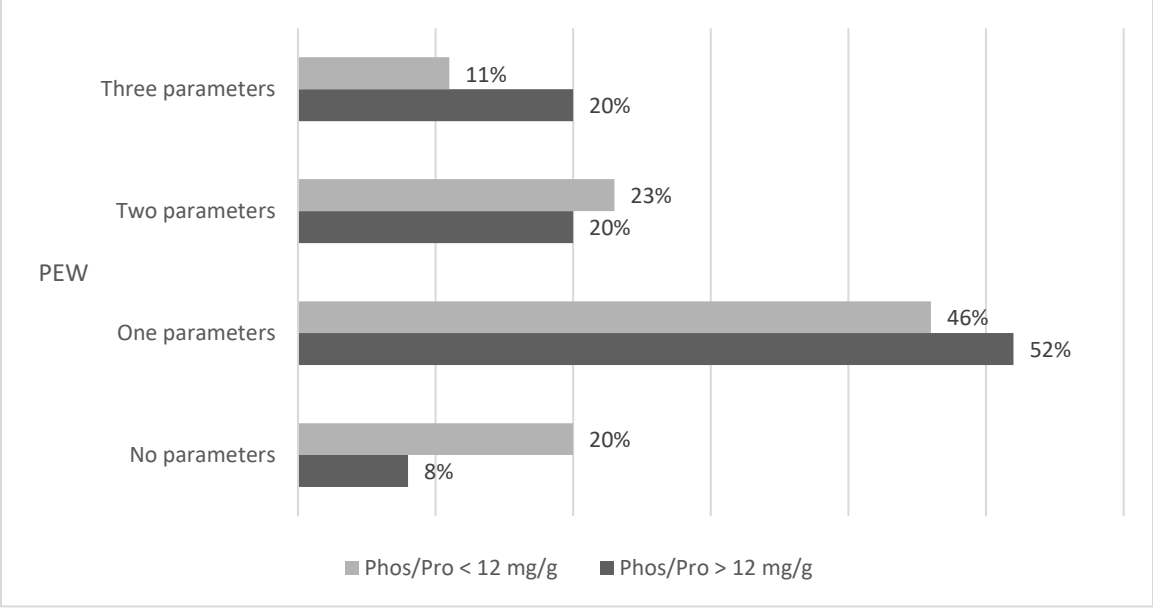
PEW

The following diagnostic criteria was used to identify patients with a PEW diagnosis:

- Alb < 3.8 mg/dL
- BMI < 23 (kg/m^2)
- MAMC < 10% (percentile of the normal population from the NHANES I study)[31]
- DEI < 25 kcals/kg

As depicted in **Figure 9**, among those patients with three diagnostic criteria for PEW a higher percentage (20%) consumed unfavorable P/pro intakes compared to 11% consuming favorable intakes. Conversely, 20% of those patients with no PEW parameters were in the favorable P/pro group in contrast to 8% in the unfavorable group. While not significant, a larger sample size may reveal greater differences in P/pro intakes among the PEW and non- PEW groups.

Figure 9 Relationship of PEW and P/pro Ratio



Pearson's Chi-Square; $p = 0.515$

Table 10 outlines PEW prevalence for both the entire population and within each ethnicity. Overall PEW prevalence in this population was calculated at 15%. In comparison to Chinese and Indian ethnicities, Malay patients exhibited the fewest clinical indicators of PEW, while 22% of Indian patients and 17% of Chinese patients had three diagnostic PEW criteria in comparison to 9% of Malay patients.

Table 10

Prevalence of PEW

Overall PEW Prevalence:	
No diagnostic PEW criteria	15%
One diagnostic PEW criteria	48%
Two diagnostic PEW criteria	22%
Three diagnostic PEW criteria	15%

PEW prevalence within Ethnicities					
Ethnicity	Number of PEW parameters (% within ethnicity)				P value
	None	**One**	**Two**	**Three**	0.110
Malay	29%	29%	33%	9%	
Chinese	10%	59%	14%	17%	
Indian	0%	67%	11%	22%	
Others	0%	0%	100%	0%	

Fisher's Exact Test

CHAPTER V: DISCUSSION

P/pro ratio

Patients consuming favorable P/pro ratios had lower serum K, lower dietary P intakes, higher dietary pro intakes, improved KDQOL physical composite scores, reduced levels of hsCRP, higher DPI, and improved serum total cholesterol. This group also showed trends towards improved measures of muscle mass and muscle strength. Noori, et. al, analyzed P/pro intakes using food frequency questionnaires (FFQs) and found that both higher dietary P intake and higher dietary P/pro ratios were each associated with increased death risk in MHD patients; however, associations between P/pro ratio on biochemical and anthropometric parameters were not addressed.[1]

A greater proportion of Chinese patients consumed favorable P/pro ratios, followed by Malay patients, whereas Indian patient's intake was of a predominantly unfavorable P/pro pattern. Favorable P/pro intakes appear to be influenced more by traditional dietary intake patterns rather than adherence to renal nutrition guidelines. Further exploration into the types of foods chosen, methods of preparation, and meal and snack patterns may reveal the underlying cause for this favorable intake of P/pro.

Measurements of muscle mass

One of the four main categories recognized in the diagnosis of PEW is muscle mass, as measured by MAMA or creatinine appearance per ISRNM guidelines. Although reduction in muscle mass is the most valid criterion for PEW diagnosis[11], the best method for taking

this measurement has been debated.[105] Accurate assessment of MAMC and MAMA requires training in anthropometry, yet it has been found that renal dietitians either lack the skills to execute these measurements or fail to take body composition measurements.[106; 107] In this study, results from both the BIA for lean and fat tissue masses and HGS, a surrogate marker of muscle strength, were positively correlated with MAMA, with BIA providing the strongest correlation. Similarly, Isoyama, et. al. found positive associations between HGS and muscle mass in a study of MHD patients with a mean age of 53.[32] The mean HGS in kg for both men and women was 21.7 and 15.1, respectively. Normative HGS for a 55-year-old right-handed male is 45.9 and 26.0 for a female,[108] approximately twice the strength than that found in this HD population. Currently, no standardized HGS tables for the HD population exists. Given the ease and minimal training required to complete BIA analysis and HGS test, consideration for use of these testing methods for the HD population has been proposed as a complementary measurement to MAC and TSF for determination of muscle mass.[35; 109]

In relation to the effects of exercise on body composition, the group of patients who reported exercising had lower fat mass and BMI, and slightly higher HDL, serum albumin and hsCRP; however, exercise did not improve their measures of muscle mass (lean tissue mass and HGS). Our findings contrast reports that exercise, particularly resistance training, improves muscle mass in HD patients; however, most published studies examining the anabolic effect of exercise on muscle mass involve a younger HD population.[110; 111] Given the median age of our study group was 55 years, sarcopenia related muscle wasting may have offset the anabolic benefits derived from exercise.

PEW

Fouque, et, al. reported that 18–75% of ESRD patients exhibit evidence of PEW;[11] we found a similar PEW prevalence of 15%, with 22% of the patient population presenting two PEW criteria and 48% with at least one diagnostic criteria.

No difference was found in the overall caloric intake between the favorable and unfavorable P/pro groups. Both groups had an average consumption of less than 25 kcals per kg. Per the IRSM guidelines for diagnosing PEW, an unintentional low dietary energy intake of < 25 kcal/kg/day is one of the criteria in diagnosing PEW. Lower DEI and DPI found in this Malaysian population produced slightly higher DEI for both genders and lower DPI for men than that found in the HEMO study (DEI and DPI for men and women in the HEMO study: 23.8 ± 8.4 and 21.7 ± 8.1, 0.97 ± 3.6 and 0.90 ± 3.4, respectively)[40] In this study, an analysis was also completed using DPI in lieu of DEI in identifying PEW patients; however, results did not produce significant differences.

Limitations of the Study

This study has several limitations. Estimation of total P intake was used in this analysis since current nutrient databases do not distinguish between sources of inorganic and organic P. The sample size was small, and a larger size may have been necessary to produce statistically significant results between favorable P/pro intakes and PEW parameters. Given patients typically underreport foods eaten, the values derived from dietary recalls may have underestimated nutrient intakes, impacting identification of

patients with PEW indices. Only one biomarker of inflammation (hsCRP) was measured; additional inflammatory markers, such as ferritin, interleukin 6 (Il-6) and tumor necrosis factor alpha (TNF-α) may have revealed stronger associations between P/pro ratio and PEW parameters or have provided a biomarker in patients identified in exhibiting PEW characteristics.

Conclusions and Recommendations

A mixed diet contains approximately 12–14 mg of P per gram of pro. Based on an upper limit of 12 mg/g P/pro used to distinguish foods with a favorable ratio, a P pyramid has been proposed by D'Alessandro, et. al. as a tool in dietary P management for CKD patients.[82] By analyzing differences between favorable (< 12 mg/g P/pro) and unfavorable (> 12 mg/g P/pro) intakes within this Malaysian HD study group in relation to various biochemical and body composition parameters, it was found that favorable P/pro intakes are inversely associated with PEW parameters of muscle mass and DPI. Both Chinese ethnicity and exercise habits appear to drive favorable P/pro intakes. A secondary outcome from this study includes findings that, when compared to measurements of MAMA, both BIA analysis and HGS are both valuable markers for lean body mass. A larger data set of HGS for the HD population would provide a valuable standard reference for the identification of reduced muscle mass, which may be considered when diagnosing PEW.

Recommendation for future studies include data collection from a different ethnic group, such as an African American population from the United States, to analyze differences in both clinical care, PEW parameters, P/pro ratio, and the ethnic influences on food intake

patterns. Additionally, a larger data set of HGS for the HD population would contribute to standardized tables for the identification of reduced muscle mass, which may be considered when diagnosing PEW.

In the Malaysian clinics, there was no restriction on eating during the HD session, a practice which may allow for improved nutritional status. In contrast, US clinics follow stricter guidelines in allowing patients to eat while on HD.[112] Patient education practices differ between countries as well. The patient load per dietitian in the Malaysian non-governmental organization (NGO) clinics was approximately 1 to 500, as opposed to the median average in the United States of 1 to 150.[43] Examining the differences between counseling approaches, education provided, patient behaviors, PEW parameters, and P/pro ratio remains largely unexplored.

Educating HD patients about P containing food additives has been shown to reduced serum P levels.[113] Examination of several written renal diet educational materials from both the Academy of Nutrition and Dietetics' Nutrition Care Manual and the National Institute of Health's National Kidney Disease Education Program (NKDEP) reveal that phosphorus additives are addressed; however, information on the bioavailability of legumes, nuts, seeds, and chocolate is not included, as these foods are listed only as high in P. Additionally, neither the aforementioned materials, nor the phosphorus food pyramid provides information on yeast leavened breads as a lower P choice over quick breads leavened with baking powder. Gaps in nutrition education provided to HD patients related to P/pro ratio and P bioavailability, coupled with a potentially over restrictive diet and high pill burden that may lead to poor diet/binder adherence, diminished intakes of protein and

lower intakes of antioxidant rich foods – factors implicated in hyperphosphatemia, PEW, and increased all cause and cardiovascular mortality -- warrant further exploration with a larger sample size. Should this larger sample demonstrate that favorable P/pro intakes are associated with improved parameters of PEW, education with emphasis in choosing foods based on the ratio of P/pro, rather than limiting foods based on P content alone, may be warranted.

Furthermore, identification and validation of prognostic nutritionally related biomarkers such as FGF-23, Fetuin A, and interleukin 6 (IL-6), remains an area of research that requires full scale testing.[114] Additionally, potential use of an "omics" approach is emerging as a promising method to identify new biomarkers in the pathogenesis of PEW and phosphate control.[115]

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Abstract

RELATIONSHIPS OF DIETARY PROTEIN AND PHOSPHORUS WITH PROTEIN ENERGY WASTING IN HEMODIALYSIS PATIENTS

by

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Both higher dietary phosphorus intake and a greater dietary phosphorus to protein ratio are associated with increased death risk in hemodialysis (HD) patients even after adjustments for serum phosphorus, type of phosphate binder used, and dietary protein, energy, and potassium intake. Furthermore, dietary phosphorus restriction to control serum phosphorus is often associated with a reduction in protein intake, which is associated with muscle wasting and poor survival. One highly prevalent complication of end stage renal disease is protein energy wasting (PEW), a state of decreased body protein and fat mass, which is strongly associated with increased morbidity and mortality in the HD population.

In a cross sectional study of 60 Malaysian HD patients, the extent to which diet composition associated with PEW parameters (serum chemistry, body mass, muscle mass, and dietary intakes), was analyzed.

It was found that favorable phosphorus to protein (P/pro) intake was inversely associated with PEW parameters of muscle mass and dietary protein intake. Both Chinese ethnicity

and exercise habits appear to drive favorable P/pro intakes. A secondary outcome from this study included findings that, when compared to measurements of mid-arm muscle area, both bio impedance analysis and hand grip strength were both valuable markers for lean body mass.