UNIVERSITI PUTRA MALAYSIA

ASSOCIATIONS BETWEEN SOCIODEMOGRAPHIC, CLINICAL FACTORS, NUTRITIONAL STATUS, DIETARY FACTORS AND BONE QUALITY WITH SERUM PHOSPHATE LEVEL AMONG HEMODIALYSIS PATIENTS

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BY

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A project submitted as a partial fulfilment of requirement for the degree of Bachelor of Science (Dietetics) from Faculty of Medicine and Health Sciences, Universiti Putra Malaysia.

This project entitled "association between sociodemographic, clinical factors, nutritional status, dietary factors and bone quality with serum phosphate level among hemodialysis patients" was prepared by Ng Pee Chien and submitted to the Faculty of Medicine and Health Sciences as a partial fulfilment of the requirement for the degree of Bachelor of Science (Dietetics) from Faculty of Medicine and Health Science, Universiti Putra Malaysia.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

ASSOCIATIONS BETWEEN SOCIODEMOGRAPHIC, CLINICAL FACTORS, NUTRITIONAL STATUS, DIETARY FACTORS AND BONE QUALITY WITH SERUM PHOSPHATE LEVEL AMONG HEMODIALYSIS PATIENTS.

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Hyperphosphatemia is the main cause of morbidity and mortality in chronic kidney disease patients. This study aimed to determine the associations between sociodemographic factors, clinical factors, nutritional status, dietary factors and bone quality with serum phosphate level among hemodialysis (HD) patients. This was a cross-sectional study involved 99 hemodialysis patients. Interviewer-administrated questionnaire was used to obtain information on sociodemographic and clinical factors. Body mass index (BMI), serum albumin and serum phosphate were retrieved from medical records as secondary data. Besides, two-day dietary data was obtained on non-dialysis day (using diet recall) and dialysis day (using food record). Bone quality of patients was determined using Quantitative ultrasound measurement on the radial part of non-dialysis arm. Statistical Package for Social Sciences (SPSS) version 24 was used in data analysis, with significant level set at $p < 0.05$. The mean age and dialysis duration of patients were 56.0 + 11.0 years old and 65.29 + 53.75 months, respectively. The prevalence of hyperphosphatemia was high with approximately 80% of the patients had high serum phosphate level. About half of the patients were either overweight or obese. Dietary protein intake was unsatisfactory with 87.9% had inadequate intake. Despite a majority of the patients (74.7%) claimed themselves complied with phosphate binder prescription, this results should be interpreted cautiously in view of the high prevalence

of hyperphosphatemia and excessive dietary phosphorus intake among the patients. There was approximately half of the patients with low bone quality while mean dietary acid load (DAL) was higher than previous studies. On the other hand, serum phosphate level was correlated negatively with age (r=-0.365, p<0.001) but associated positively with educational level (χ^2= 15.725, p<0.001) and compliance to phosphate binder (r= 5.929, p= 0.021). **Conclusion**: Hyperphosphatemia was prevalent among HD patients which deserve attentions from relevant authorities. Poorer serum phosphate level among younger patients and educated patients is not uncommon, which signify the attention of healthcare professional including dietitians to be sensitive with the serum phosphate compliance of young and or educated patients. Despite there were no significant associations found between serum phosphate levels and dietary acid load and bone quality, the high prevalence of poor bone quality and high DAL among the HD patients deserve more studies in the future on these relatively under-studied aspects.

ABSTRAK

HUBUNGAN ANTARA SOSIODEMOGRAFIK, FAKTOR CLINICAL, STATUS PEMAKANAN, FAKTOR PERMAKANAN DAN QUALITI TULANG DENGAN SERUM FOSFAT DALAM KALANGAN PESAKIT HEMODIALISIS.

NG PEE CHIEN

Hiperfosfatemia adalah penyebab utama morbiditi dan kematian dalam kalangan penyakit buah pinggang kronik. Kajian ini bertujuan untuk mengetahui perkaitan antara faktor sosiodemografi, faktor klinikal, statuspemakanan, faktor pemakanan dan kualiti tulang dengan tahap fosfat serum dalam kalangan pesakit hemodialisis (HD). Ini adalah kajian keratan rentas yang melibatkan 99 pesakit hemodialisis. Soal selidik yang ditadbir oleh penemuduga digunakan untuk mendapatkan maklumat mengenai faktor sosiodemografi dan klinikal. Indeks jisim badan (BMI), albumin serum dan serum fosfat diambil dari rekod perubatan sebagai data sekunder. Selain itu, data diet dua hari diperoleh pada hari tidak menjalanin dialisis (menggunakan diet ingat) dan hari dialisis (menggunakan catatan makanan). Kualiti tulang pesakit ditentukan menggunakan pengukuran ultrasound kuantitatif pada bahagian radial lengan bukan dialisis. Statistical Package for Social Sciences (SPSS) versi 24 digunakan dalam analisis data, dengan signifikan ditetapkan pada $p < 0.05$. Puratar umur dan tempoh dialisis pesakit masing-masing adalah berumur 56.3 tahun dan 65.29 bulan. Prevalen hiperfosfatemia adalah tinggi dengan kira-kira 80% pesakit mempunyai tahap fosfat serum yang tinggi. Kira-kira separuh daripada pesakit mempunyai berat badan berlebihan atau gemuk. Pengambilan protein diet tidak memuaskan dengan hampir satu daripada sembilan pesakit mempunyai pengambilan yang tidak mencukupi. Walaupun kebanyakan pesakit

(74.7%) mengakui mematuhikepada presripsi pengikat fosfat, hasil ini harus ditafsirkan dengan berhati-hati memandangkan tingginya prevalen hiperfosfatemia dan pengambilan fosforus makanan yang berlebihan di kalangan pesakit. Terdapat kira-kira separuh daripada pesakit dengan kualiti tulang yang rendah sementara purata asid diet (DAL) lebih tinggi daripada kajian sebelumnya. Sebaliknya, aras fosfat serum berkorelasi negatif dengan usia ($r = -0.365$, $p < 0.001$) tetapi dikaitkan positif dengan tahap pendidikan ($\chi^2 = 15.725$, $p < 0.001$) dan kepatuhan terhadap pengikat fosfat ($r = 5.929$, $p = 0.021$). **Kesimpulan**: Hiperfosfatemia berlaku di kalangan pesakit HD patut mendapat perhatian daripada pihak berkuasa yang berkaitan. Tahap fosfat serum yang lebih tinggi dalam kalangan pesakit yang lebih muda dan pesakit yang berpendidikan tidak jarang berlaku, yang memerlukan perhatian daripada profesional kesihatan termasuk pakar diet untuk lebih peka terhadap pematuhan serum fosfat untuk pesakit muda dan berpendidikan. Walaupun tidak terdapat hubungan yang signifikan antara tahap fosfat serum, asid makanan dan kualiti tulang, kualiti tulang yang rendah dan asid makanan yang tinggi dalamkalangan pesakit HD memerlukan lebih banyak kajian pada masa akan datang mengenai aspek yang kurang dikaji ini.

CHAPTER 1

INTRODUCTION

1.1 Study Background

Kidneys are bean-shaped organs which play critical role in health of an individual. Kidneys perform several important functions including to excrete waste products, extra fluid, acid produce from the body and homeostasis of salt, water and minerals including sodium, phosphate, potassium and calcium in the blood. Abnormal homeostasis will affect the normal function of other organ and tissue such as nerves and muscles (Bessie Young et al., 2014). Chronic kidney disease is characterized by an irreversible deterioration of renal function that gradually progresses to end-stage kidney disease (ESKD), representing by glomerular filtration rate (GFR) less than 15 mL/min per 1.73 m^2. At this stage, there is only minimal kidney function, with patients require renal replacement therapies to sustain life. Treatment mortalities for ESKD are dialysis or kidney transplantation (Webster, Nagler, Morton, & Masson, 2017). In Malaysia, prevalence of CKD is 9.07% of the whole population with 0.36% at CKD stage 5 or ESKD (Ismail et al., 2016).

There are two types of dialysis treatment namely peritoneal diaysis and hemodialysis. Peritoneal dialysis is preferred in countries such as Hong Kong (Yu, Chau, Ho & Li, 2007) and Mexico (Cueto-Manzano & Rojas-Campos, 2007) while hemodialysis remains as main treatment modality for ESKD in Malaysia (Lim, Ong & Goh, 2011) and other countries (Tan et al., 2015 ; USRDS, 2009). In light of the multiple functions play by kidneys, patients with ESKD are often presented with complications including acid base imbalance, anemia and hyperphosphatemia.

Hyperphosphatemia is common in ESKD due to impaired renal phosphate excretion (Malberti, 2013). Hyperphosphatemia in CKD patients is a potentially life altering condition that can lead to cardiovascular calcification (Dhingra et al., 2007), metabolic bone disease (renal osteodystrophy), development of secondary hyperparathyroidism and increased risk of cardiovascular diseases and mortality rates (Askar, 2015; Floege et al., 2011; Shaman & Kowalski, 2016). Good adherence to phosphate binder medication therapy, dietary restriction, and dialysis prescription are required for the optimal management of hyperphosphatemia (Malberti, 2013). Despite oral phosphate binders in conjunction with dietary phosphate restriction, can ameliorate hyperphosphatemia in patients with chronic kidney disease, particularly those on dialysis (Chan et al., 2017), hyperphosphatemia remains prevalent among hemodialysis patients. High prevalence of hyperphosphatemia was shown from previous studies, ranging from 60.5% to 73.8% (Rabbani & Rao, 2017; Afifi et al., 2005; Block & Port, 2000; Llach, 1999).

1.2 Problem Statement

Over the past two decades, despite a bourgeoning body of research has focused on the epidemiology, causes, consequences, and treatment of hyperphosphatemia, which has advanced our understanding of the manifestations and management on this medical issue, hyperphosphatemia remains common among ESRD patients undergoing for hemodialysis (Chan, Zalilah & Hii, 2012). Several factors had been proposed being the determinants of hyperphosphatemia including socialdemographic factors but findings remain inconsistent. For example, while Chan et al (2012) showed younger, male, working patients and those with longer duration on hemodialysis has higher serum phosphate, similar findings failed to be observed in other studies (Afifi et al., 2015; Collinson et al., 2014; Mehrotra, Rishishwar & Sharma, 2015).

Besides hyperphosphatemia, poor nutritional status is highly prevalent among hemodialysis patients. Malnutrition among hemodialysis is multifactorial in nature, with dietary factor being one of the strong determinants. While trying to restrict dietary phosphorus intake, patients may develop protein-energy wasting (Noce et al., 2016), as foods high in phosphate such as meats, eggs and dairy products are generally rich in protein. Previous studies showed low serum phosphate was correlated with low serum albumin, low body mass index (Lee et al., 2017, Garagarza et al., 2017) and increased risk of malnutrition (Pourhassan, Müller, Volkert & Wirth, 2019). However, inconsistency in findings exist in other study (Moore et al., 2015). On the other hand, dietary phosphorus and protein intake were positively correlated with serum phosphate level in other population (Mart et al., 2001; Moore et al., 2015; Shinaberger et al., 2008). Nonetheless, the correlation between dietary phosphorus intake and serum phosphate concentration was reported to be weak (Noori et al., 2010). In light of lacking of such

information at the local context, this signifies the need for more studies in this aspect. More recently, a modest body of research, including animal studies, observational epidemiology and clinical trials, has examined the potential role of the dietary acid load (DAL) in patients with CKD (Scialla & Anderson, 2013). Recent study reported a positive association between acid load and circulating serum phosphate concentration in the United States CKD population (Khairallah et al., 2017). There is no study available locally and thus warrant for the needs of studies on this aspect at the local context.

It is generally acknowledged that good adherence to phosphate binder, dietary restriction, and dialysis prescription are crutial for the optimal management of hyperphosphatemia (Malberti, 2013). Better compliance to phosphate binder was found to be correlated with lower phosphate levels (Chan et al., 2012; Wileman et al., 2015). Study by Chiu (2009) however showed no correlation between phosphate binder adherance and serum phosphate levels, making a definite conclusion unable to draw.

Among CKD's patient, mineral and bone disorders are common (Nigwekar, Tamez & Thadhani, 2014). Body phosphate homeostasis is depending on extracellular exchange of phosphate and bone storage pool, dietary phosphate absorption in the gut, renal phosphate reabsorption and excretion by the kidney (Penido & Alon, 2012). As bone turnover rate increases, the release of calcium and phosphorus from bone into circulation also increases. This lead to vascular medial calcinosis and increase in parathyroid hormone and phosphaturic hormone FGF23 to compensate with the rise in phosphorus (Suki & Moore, 2016). Previous research showed serum phosphate was positively related to fracture risk in both men and women in healthy population (Campos-Obando et al., 2017), and was significantly associated with hospitalization due to fracture in hemodialysis patients (Block et al., 2004). There is however unclear and limited finding regarding serum phosphate level and bone quality locally. Taking all

together, there is scarcity of data available on how dietary factor, nutritional status or bone status may affect the serum phosphate level among hemodialysis patients, which reflected the research gaps tried to be closed in the current study.

Research Questions

1.What are the prevalence of hyperphosphatemia among hemodialysis patients?

2. What are the sociodemographic factors and clinical factors among hemodialysis patients?

3. How is the nutritional status among hemodialysis patients?

4. How are the intakes of dietary protein and phosphorus among hemodialysis patients?

5. Do hemodialysis patients consume a high dietary acid load pattern?

6. How is the bone quality among hemodialysis patients?

7. Are there associations between sociodemographic factors, clinical factors, nutritional status, dietary factors, bone quality and serum phosphate level among hemodialysis patients?

1.3 Significance of study

Abnormal phosphate homeostatis is often associated with higher risk of cardiovascular mortality in hemodialysis patients, which deserves extensive research. This study was carried out to provide additional or new knowledge on factors that may associated with hyperphosphate. Finding of the study will aid in the prevention and proper planning of interventions by health care professional to improve hyperphosphatemia issue among hemodialysis patients. Findings of this study may also be used as baseline data for future research.

1.4 Objectives

1.4.1 General Objective

To determine the associations between sociodemographic factors, clinical factor, nutritional status, dietary factors and bone quality with serum phosphate level among hemodialysis patients.

1.4.2 Specific Objectives

1. To determine the following among hemodialysis patients

a. Sociodemographic factors (age, sex, ethnicity, education level, marital status, employment status) and clinical factors (dialysis duration, compliance on phosphate binders)

b. nutritional status (body mass index, serum albumin)

c. dietary intake of protein, phosphorus and dietary acid load

d. bone quality

2. To determine the prevalence of hyperphosphatemia among HD patients

3. To determine the associations between sociodemographic factors, clinical factors, nutritional status, dietary factors, bone quality and serum phosphate level among hemodialysis patients.

1.5 Alternative Hypotheses

1. There are significant associations between sociodemographic factors, clinical factor, nutritional status, dietary factors, bone quality and serum phosphate level among hemodialysis patients.

1.6 Conceptual Framework

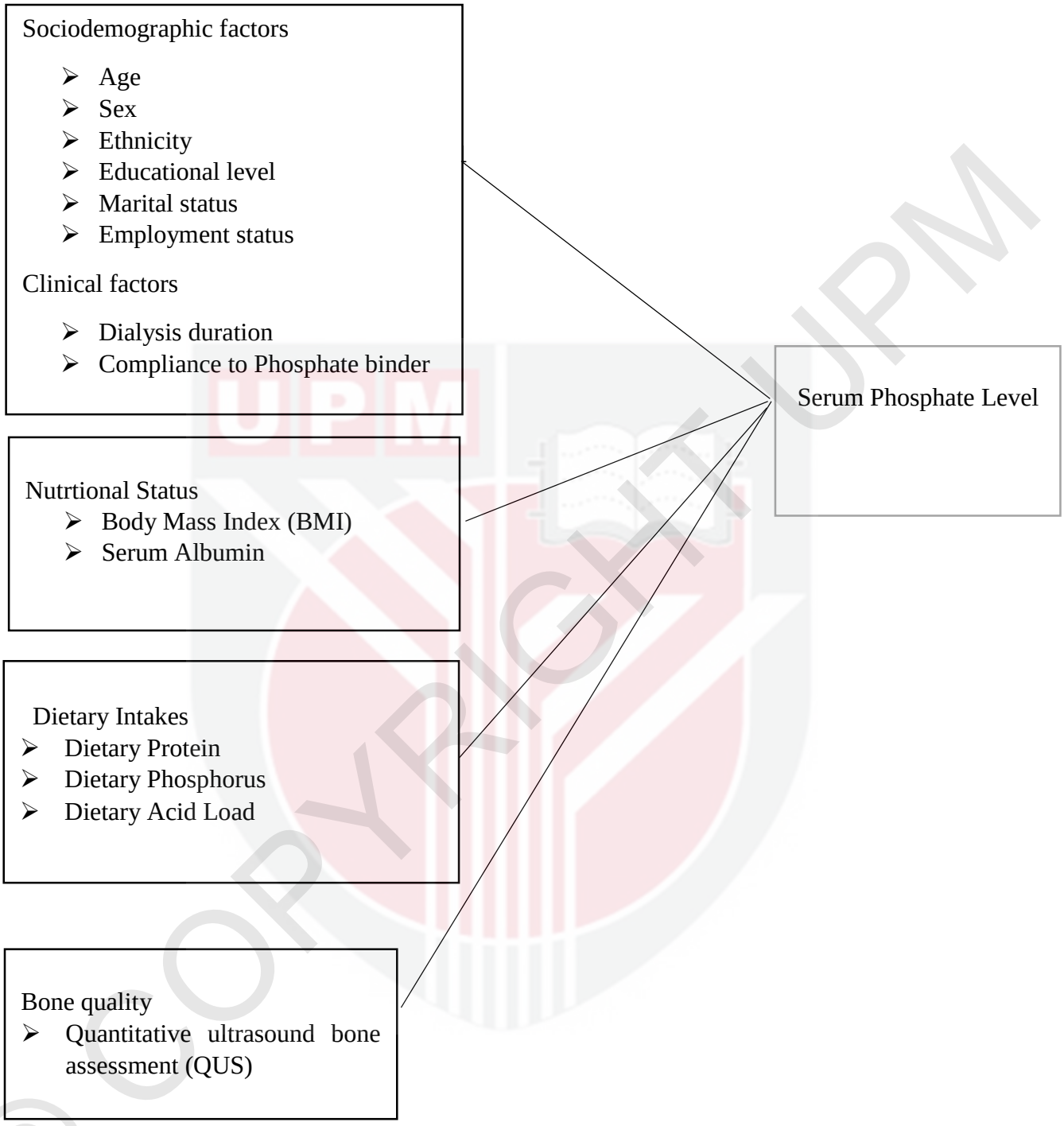

Figure 1: Conceptual Framework

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of Chronic Kidney Disease (CKD)

Chronic kidney disease refer to heterogeneous disorders affecting structure and function of kidney. Early stage of CKD usually asymptomatic, reversible and detected during comorbid disorders assessment. Rapid progressive of CKD can cause kidney failure within months, but other diseases develop gradually over decades with no progress after long term follow-up. CKD is defined with presence of kidney damage or reduced in function of kidney which is glomerular filtration rate, GFR < 60 mL/min per 1.73 m^2 for 3 months or above. CKD is classified into five stages according to the GFR as depicts in Table 1 below:

Table 1: Classification of CKD

	GFR descriptors and range	**Range (mL/min/1·73m^2)**
G1	Normal or high	≥90
G2	Mildly decreased	60–89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	< 15

Source: Levey & Coresh (2012)

There are some pathological abnormalities for CKD where the clinical diagnosis is according to the pathology and cause. For example, glomerular diseases including diabetes, autoimmune diseases, systemic infections, drugs and neoplasia. For vascular diseases, the pathological abnormalities are atherosclerosis, hypertension, ischaemia, vasculitis, thrombotic and microangiopathy. Besides that, tubulointerstitial diseases such as urinary-tract infections, stones, obstruction and toxic effects of drugs, whereas cystic disease include polycystic kidney disease. Kidney damage are also shown by the condition of albuminuria. When urine albumin to creatinine ratio (ACR) is more than 30 mg/g, it will increase the glomerular permeability. The normal range for ACR is <10 mg/g. For categories of 10-29 mg/g, ACR is categorized as high normal, 30-300 mg/g is high and >300 mg/g is very high. Symptoms of nephrotic syndrome such as low serum albumin, high serum cholesterol and oedema will be present when urine ACR > 2000 mg/g (Levey & Coresh, 2012).

Kidney failure is considered the most severe outcome of chronic kidney disease and the symptoms usually present by the complications of decreased kidney function. In severe cases which is end-stage renal disease, it can only be treated by dialysis and kidney transplantation. Developmental of CKD is related to old age, diabetes, cardiovascular disease, obesity, hypertension with diabetic glomerulosclerosis and hypertensive nephrosclerosis as the pathological signs (Levey & Coresh, 2012). In most countries, the main cause of kidney failure is diabetes with new patients of 40% or more (Kepler, 2010).

2.2 Hyperphosphatemia

The second most abundant mineral in human body is phosphorus and majority (85%) is in the form of bone and teeth as hydroxyapatitie compounds. The other 14% is found intracellularly in the form of organic phosphate while 1% is the extracellular inorganic phosphate. Inorganic phosphate is important as the component of many other organic compounds and functions in the cell structures including phospholipid membranes, nucleic acid and phosphoproteins. Cell signalling, energy metabolism, bone mineralisation, membrane functions, formation of nucleic acid and carbohydrate metabolism are influence by phosphate (Shaman & Kowalski, 2016). Hyperphosphatemia is common in late stages of CKD (Locatelli et al., 2014). The main cause of morbidity and mortality in CKD patients is hyperphosphatemia (Askar, 2015). Cardiovascular diseases are responsible for half of the deaths in End Stage Renal Disease (ESRD) patients. For example, cardiac death, ischemic heart disease, heart failure and peripheral arterial disease (Giachelli, 2004). The cardiovascular complication significantly related to vascular calcification which is caused by hyperphosphatemia, increased in calcium x phosphorus production, elevated calcium load in diet and dialysate (Block et al., 2004). Decreased kidney function of 25 to 30% may lead to phosphorus retention and hyperphosphatemia. Then, it will cause the rise of abnormalities in metabolism of vitamin D and affect the parathyroid gland function and evolve of secondary hyperparathyroidism and mixed renal osteodystrophy. In addition, hyperphosphatemia also cause rise in fibroblast growth factor- 23 levels and vascular calcification which independently related with adverse cardiovascular outcomes and mortality (Lertdumrongluk et al., 2013).

The mechanism in regulation of phosphate homeostasis is by the parathyroid gland and involved kidney and bone in the process. When the extracellular calcium ion

level fluctuates and detected by parathyroid calcium-sensing receptors (CaSRs), the regulation of synthesis and secretion of parathyroid hormone (PTH) will take place (Felsenfeld, Rodríguez & Aguilera-Tejero, 2007). PTH will acts on bone to increase the release of calcium and phosphate. It will also signal kidney to decrease the urinary calcium excretion, inhibit absorption of phosphate and stimulate 1,25-hydroxyvitamin D (1,25$(OH)_2$D) production. A rise in 1,25$(OH)_2$D will lead to more calcium and phosphate absorb from the dietary, stop the negative feedback loop by inhibit PTH production by the parathyroid gland (Silver et al., 1986; Okazaki, Igarashi & Kronenberg, 1988). The function of PTH to increase phosphate excretion through 1,25 $(OH)_2$D-mediated dietary phosphate absorption and phosphate release from the bone is offsets. Increase in serum phosphate will promote release of PTH on kidney via putative extracellular phosphate sensor to promote phosphaturia and prevent hyperphosphatemia (Silver & Naveh-Many, 2009). However, the mechanism in reduced renal function of CKD patients is not well regulated leading to commonly high serum phosphate level among them.

Treatments of hyperphosphatemia include dietary phosphate restriction follow by effective dialysis and also phosphate binders. Dietary phosphate restriction including protein restriction, avoid dairy products and also phosphate additives such as roast breast turkey or chicken and cooked ham. High phosphate content beverage need to be more concern as it is completely absorbed by the intestinal tract (Benini et al., 2011).

2.3 Factor associated with Serum Phosphate Level

2.3.1 Sociodemographic factors

There are inconsistent finding regarding sociodemographic factors and serum phosphate level. Earlier studies showed age was negatively correlated with dietary compliance where the more advanced age, the better the compliance to therapeutic treatment (Chan et al., 2012; Collinson et al., 2014). For sex, while Chan et al (2012) found female was correlated to dietary restriction than male, there had been inconsistency in findings. Mehrotra, Rishishwar & Sharma (2015) showed hyperphosphatemia is equally present in both male and female patients. For employment status, earlier local study showed working subjects had higher non-compliance to dietary restrictions (Chan et al., 2012).

2.3.2 Nutritional status

Protein-energy wasting is common among CKD patient with presence of low serum albumin level or transthyretin, weight loss and sarcopenia with strong correlation to mortality among CKD patients (Kovesdy, Kopple & Kalantar-Zadeh, 2013). Previous study showed patients with high serum albumin had 32% lower risk of low serum phosphate level (Lee et al., 2017). Similarly, higher Body Mass Index (BMI) was found to be associated with reduced risk of low serum phosphate (Lee et al., 2017). A recent study among older hospitalized patients demonstrated malnutrition was correlated with hypophosphatemia (Pourhassan, Müller, Volkert & Wirth, 2019), suggesting serum phosphate level may act as a nutritional risk indicator. Earlier study among Portuguese HD patients also showed hypophosphatemia was correlated with lower albumin level, BMI and body cell mass index, fat tissue index and lean tissue index, and lower survival

rates than normo and hyperphosphatemia patients (Garagarza et al., 2017). The serum phosphate recommended in HD patients is between 3.5 – 5.5 mg/dL (Massry et al., 2003).

2.3.3 Dietary Intakes

(a) Dietary Protein and Dietary Phosphate

Dietary phosphate sources include organic phosphorus from plant and animal source of protein and inorganic phosphorus from additives contained in processes food. Besides the phosphorus content, the bioavailability of phosphorus should be considered in the management of serum phosphate level. The bioavailability of phosphorus in plant foods (20-40%) and animal protein (40-60%) is lower than those from the inorganic phosphorus (phosphate additives has 100% bioavailability), at such high intake of inorganic phosphorus is expected to increase serum phosphate level or cause hyperphosphatemia significantly among CKD patients (Umeukeje, Mixon & Cavanaugh, 2018). Unfortunately, nutritional labelling of phosphate inorganic is not mandatory. This coupled with the unavailable of inorganic phosphate in most of the database of food composition analysis further complicate the good compliance of serum phosphate level among CKD patients.

As food rich in protein are often rich in phosphorus, hence there is almost linear relationship found between intakes of dietary protein and phosphorus **(**Rufino et al., 1998). High protein diet are recommended for CKD patients undergoing for dialysis to compensate the amino acid loss from routine dialysis procedure. Theoritically, a recommended protein intakes of 1.0-1.3 g/kg/day will contribute to 800-1400 mg/day of

dietary phosphate intakes with 60-70% of net phosphate absorption from the total intake (Rocco, Easter & Makoff, 1999). The absorption will increase to 86% of dietary phosphate if calcitriol is used and reduce to 30-40% if ingested with proper dosage of phosphate binder medication (Rocco, Easter & Makoff, 1999). Twice weekly hemodialysis with high-efficiency and high-flux dialyzer will removes about 900 mg of phosphate. Due to phosphate efflux slowly from intracellular to extracellular compartments, serum phosphate starts to rebound in a typical four hours dialysis session (Winchester et al., 1993). Thus, patients may be treated further with erythropoietin (EPO) for phosphate clearance. However, even patients with adequate dialysis and compliance to phosphate binder, they still have a net positive phosphate balance (Lim, Flanigan & Fangman, 1990), which emphasize the need for dietary phosphate restriction among hemodialysis patients. Nevertheless, dietary management of phosphorus is challenging in lieu of dietary protein sources are high in phosphorus as well. Patients need to be educated on how to juggle dietary intake to ensure adequate protein intake to minimise risk of malnutrition and at the same time can avoid excessive intake of phosphate.

(b) Dietary Acid Load

Kidney plays an important role in maintaining acid-base homeostasis by excreting acid as either in the form of ammonium or as titratable acids which use phosphate as a buffer. As kidney function declines in CKD, excretion of titratable acid in the form of monovalent phosphate may be relatively increased through reduction in urine pH or augmented phosphaturia, to overcome lower acid excretion in the form of ammonium (NH_4^+). Besides, fractional phosphorus excretion may be augmented by the PTH and FGF-23, to prevent hyperphosphatemia. However, ammoniagenesis is not function effectively in CKD patients which promotes metabolic acidosis to occur.

In general, acid load refers to net acid excretion (calculated from urine ammonium, pH, phosphorus and creatinine) and potential renal acid load (PRAL) which can be calculated from the dietary intakes of protein, phosphate, calcium, potassium, magnesium, and chloride (Remer, 2000). Earlier animal models suggest that changes in acid-base status and acid load may affect phosphorus homeostasis (Ambuhl et al., 1998; Burki et al., 2015; Krieger et al., 2012). Animal and human studies have evaluated integrated acid-base and phosphorus physiology relevant to early or moderate CKD when overt metabolic acidosis is uncommon, but adaptations to increase titratable acidity may already be occurring (Burki et al., 2015; Scialla et al., 2017). More recently, Khairallah et al. (2017) found higher acid load associated with circulating phosphorus and augmented phosphaturia. This aspect is highly understudied either locally or internationally.

2.3.4 Clinical Factors

One of the treatments to hyperphosphatemia is phosphate binder medication therapy (Malberti, 2013). In order to reduce morbidity and mortality risk in ESRD patients, optimal use of phosphate binder is important to maintain serum phosphate levels in normal range of 3.5 – 5.5 mg/dL (Arenas et al, 2010; Isakova et al., 2017). Nevertheless, about 74% of patients are estimated as noncompliant to phosphate binder medication (Schmid, Hartmann & Schiffl, 2009; Karamanidou et al., 2008). The barriers to adherence of phosphate binder are high pill counts, adverse side effects, complex adjustable schedules, financial burden, limited knowledge on the importance of phosphate binder medication and emotional support for patients (Covic & Rastogi, 2013; Ghimire et al., 2015). Other barriers are the disruption of binder medication due to

recurrent hospitalizations and the overall burden and complexity of medication where patients need to take diabetes and hypertension medication too (Ghimire et al., 2015).

Previous study showed no correlation between adherence to phosphate binder medication and serum phosphate levels (Chiu, 2009). Physician prescribes larger number of phosphate binder medication in order to encounter for the high serum phosphate level. However, this will lead to higher pill burden that contributed to the non-adherence of phosphate binder among patients and increasing the pill may not be appropriate measure to treat hyperphosphatemia in large number of patients (Chiu, 2009). In contrast, there was inconsistent finding states that higher compliance to phosphate binder is correlated with lower phosphorus levels (Chan et al., 2012; Wileman et al., 2015). Controlling serum phosphate level within normal range is important to reduce the risk of cardiovascular diseases (CVD) associated with hyperphosphatemia as CVD are primary death causing disease among dialysis patients (Block et al., 1998).

Besides, patients with long duration of dialysis tend to has higher serum phosphate level (Chan et al., 2012; Isakova et al., 2009), with findings inconsistencies in other study (Afifi et al., 2005). Furthermore, hypophosphatemia was correlated significantly with better dialysis adequacy and higher age (Garagarza et al., 2017). The inconsistent in finding warrants for more research to be carried out.

2.3.5 Bone Quality

Hyperphosphatemia is common in ESRD and high phosphate level is an important component in mineral and bone disease (BMD) which increases risk of fracture and osteoporosis among CKD patients (Malberti, 2013; Slatopolsky, Gonzalez & Martin, 2003). Mineral and bone disease appears even in the early stages of CKD and alteration in vitamin D metabolism that lead to major research and clinical implications. CKD's patient may at risk of renal bone diseases which is secondary hyperparathyroidism or osteitis fibrosa cystica. This bone abnormality may be no symptom shown or the symptoms shown as bone pain or fractures. Although the result of studies of bone fracture in CKD patients have been inconsistent, dialysis patients have three to four times higher risk of hip or vertebral fractures than general population when considering for adjustment for age, race and gender (Nigwekar, Tamez & Thadhani, 2014).

Increase in serum phosphate will cause PTH production and secretion to increase and further increase 25-hydroxyvitamin D conversion to 1, 25 D by renal CYP27B1 (1α-hydroxylase) enzyme. Both PTH and 1, 25D work together to promote FGF-23 production by the osteocytes. Later, PTH and FGF23 promote more excretion of urinary phosphate through inhibiting renal sodium phosphate co-transporters (NaPi-2a and NaPi-2c) that reduce renal phosphate reabsorption. Bone reabsorption to release phosphorus and calcium is stimulated by PTH and 1, 25 D and 1, 25 D further increases the active intestinal absorption of phosphorus and calcium. The negative feedback loops to maintain homeostasis involve FGF-23 that acted on PTH and 1, 25 D and 1,25 D that promotes negative feedback on PTH and itself (Vorland et al., 2017).

Bone fractures risk is higher in CKD patients compare to the general population (Ambrus et al., 2011). From previous study, calcium-phosphate product was negatively correlated with QUS in male patients. Thus, it is suggested to control of calcium and phosphate metabolism that are important to bone health in CKD patients. However, there is no association between the all the participants (male and female) with QUS parameter (Kuo, Ho, Chang & Chu, 2010).

Extremely high serum phosphate level is related with increased risk of fracture and mineralization defects. Earlier study showed serum phosphate level was associated with hip fracture, but such association was limited to phosphate level of ≥5.5 mg/dl (Jadoul et al., 2006). More recently, a study shown that serum phosphate level was correlated positively to fracture risk with 47% higher risk of fracture (assessed using bone mineral density) with increase in each mg/dL serum phosphate level after considering the adjusted multiple covariates (Campos-Obando et al., 2017). However, this study was performed among general population and hence the application may be limited to CKD population. Similar to dietary acid load, there is limited study in this aspect, which warrants for more work to be done.

CHAPTER 3

METHODOLOGY

3.1 Study Designs

This was a cross-sectional study aimed to determine the associations between social demographic, clinical factors, nutritional status, dietary factors, bone quality with serum phosphate level among hemodialysis patients.

3.2 Study Location

There are nine districts in Selangor including Kuala Langat, Kuala Selangor, Hulu Selangor, Hulu Langat, Petaling, Sepang, Klang, Gombak and Sabak Bernam. Selangor has high number of population with 6.54 million population in 2019. (Demographic Statistics First Quarter Malaysia, 2019). Selangor is placed in the right and west of Peninsular Malaysia. It is bounded with Perak in the north, Pahang in the east, Negeri Sembilan in the south and Straits of Malacca in the west. The capital of Selangor is Shah Alam. The study will be carried out in Selangor as the it is the most populous states with the highest number of population in Malaysia. It should be suitable to represent the general population in Malaysia. Due to time constraints and transportation problem, the hemodialysis centres was chosen within 40 minutes distance from Faculty of Medicine and Health Sciences, Universiti Putra Malaysia.

3.3 Sample Size Determination

Calculation of sample size was performed by using the established equation for correlations study as shown below (Hulley et al., 2013).

$$\mathbf{N = [(Z\alpha+Z\beta)/C]^2 + 3}$$

$$C = 0.5 \times \ln[(1+r)/(1-r)]$$

Where

N= number of respondents needed

The standard normal deviate for $\alpha = Z\alpha = 1.96$

The standard normal deviate for $\beta = Z\beta = 0.84$ (80%)

r = the expected correlation coefficient

Table 2 : Calculation of Sample Size (Correlation studies)

Correlation studies	Factor	Correlation coefficient, r	Sample size, N
(Nasri & Kheiri, 2008).	Social Demographic (Age)	r= -0.28	$C = 0.5 \times \ln[(1+r)/(1-r)]$ $= 0.5 \times \ln[(1-0.28)/(1+0.28)]$ $= -0.29$ $N = [(Z\alpha+Z\beta)/C]^2 + 3$ $= [(1.96+0.84)/-0.29]^2 + 3$ $= 96$
(Chan et al., 2012).	Social demographic (employment status)	r = -0.355	$C = 0.5 \times \ln[(1+r)/(1-r)]$ $= 0.5 \times \ln[(1-0.355)/(1+0.355)]$ $= - 0.37$ $N = [(Z\alpha+Z\beta)/C]^2 + 3$ $= [(1.96+0.84)/-0.37]^2 + 3$ $= 60$
(Chan et al., 2012).	Social demographic (gender) Female	r= 0.252	$C = 0.5 \times \ln[(1+r)/(1-r)]$ $= 0.5 \times \ln[(1+0.252)/(1-0.252)]$ $= 0.26$ $N = [(Z\alpha+Z\beta)/C]^2 + 3$ $= [(1.96+0.84)/0.26]^2 + 3$ $= 119$
(Noori et al., 2010).	Phosphorus intake and Protein intake	r = 0.13	$C = 0.5 \times \ln[(1+r)/(1-r)]$ $= 0.5 \times \ln[(1+0.13)/(1- 0.13)]$ $= 0.13$ $N = [(Z\alpha+Z\beta)/C]^2 + 3$ $= [(1.96+0.84)/0.13]^2 + 3$ $= 467$
(Wileman et al., 2015)	Patient self-reported adherance	r = 0.42	$C = 0.5 \times \ln[(1+r)/(1-r)]$ $= 0.5 \times \ln[(1+0.42)/(1- 0.42)]$ $= 0.45$ $N = [(Z\alpha+Z\beta)/C]^2 + 3$ $= [(1.96+0.84)/0.45]^2 + 3$ $= 42$

On the other hand, calculation of sample size according to universal formula for prevalence study was performed as shown below (Hulley, Cummings, Browner, Grady, & Newman, 2013).

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n =sample size

Z = statistic corresponding to level of confidence, 95%, 1.96

P = expected prevalence (that can be obtained from same studies or a pilot study conducted by the researchers)

d = precision (corresponding to effect size), d= 0.1

Table 3 : Calculation of Sample Size (Prevalence studies)

Prevalence study	**Factor**	**Prevalence, p**	**Sample size, N**
(Rabbani & Rao, 2017)	Hyperphosphatemia	p =0.738	$\frac{Z^2 P(1-P)}{d^2}$ = $\frac{1.96^2(0.738)(1-0.738)}{0.1^2}$ = 74

Based on the calculations above, the highest number of sample is n= 467. However, due to financial and human resource constraints, it was difficult to obtain such big number of subjects. Thus, the second highest sample size, n = 119 was considered in this study. To consider possibility of missing data, an additional of 10% sample was added. Therefore, the total number of participants for this research was set at 131. However,

due to pandemic COVID-19 which strike the country early of this year, only 99 samples were able to be completed before the declaration of nationwide movement control order.

3.4 Respondents

Respondents involved in this study were dialysis patients who meet the inclusion and exclusion criteria as shown in the table below.

Table 4 : Inclusion and exclusion criteria for selection of respondents

Inclusion criteria	Exclusion criteria
Malaysian (All ethnicity)	Hospitalized in previous three months
Male and Female	Diagnosed with severe heart or lung failure with unstable vital signs
Aged 18 years and above	Diagnosed with Hepatitis A, B or C
Duration of dialysis more than three months	
Undergoing hemodialysis for four hours and thrice weekly	

3.5 Sampling Design

The sampling design for the study was purposive sampling. A list of dialysis centres in nine districts in Selangor was obtained from National Renal Registry. Dialysis centres in Hulu Langat and Putrajaya were selected. In the need to meet 143 sample, with approximately 30 patients at each dialysis centre, about 6 dialysis centres needed. Calls and email were sent to the dialysis centres to get approval for data collection.

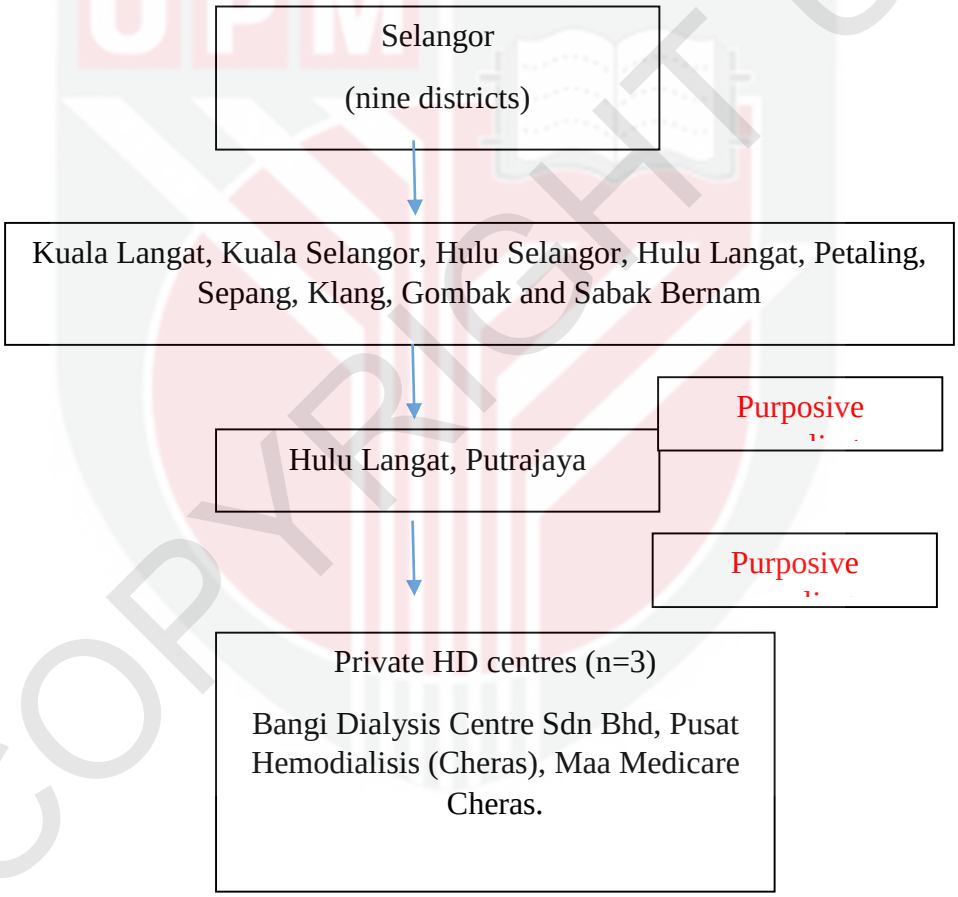

Figure 2: Flow chart of sampling method

3.6 Measures

A set of pre-tested interviewer- administered questionnaire was used as study instrument to comprehend anthropometric measurements,and Omnisense Quantitative ultrasound bone measurement was carried out. Interviewer-administered questionnaire was chosen due to the inconvenience of the participants to fill in the questionnaire during dialysis. The questionnaire comprises of sociodemographic characteristics (age, sex, ethnicity, education level, marital status, employment status), duration on dialysis, compliance to phosphate binder medication and dietary intake. Secondary data was obtained from medical records for serum albumin and serum phosphate. In addition, anthropometry data such as body mass index (BMI) and bone quality were assessed according to standard protocols.

3.6.1 Sociodemographic Characteristics

Sociodemographic factors of participants included age, sex, ethnicity, educational level, marital status and employment status were obtained using the pre-tested structured questionnaire.

3.6.2 Clinical factors

Information on duration on dialysis was obtained from patients' medical records as secondary data. On the other hand, compliance of patients on phosphate binder was assessed. To indicate the non compliance percentage, question asked was " how many times in the past week (7 days) you skip your phosphate binder? " The information about quantity of medication given to patients and number of days supplied from each filled prescription are collected to calculate the percentage of compliance using formula below:

Percentage of compliant to phosphate binder:

$$\frac{\text{Total dose for a week} - \text{how many times skipped in a week}}{\text{Total dose for a week}} \text{ X100\%}$$

Patients were considered as complied when the percentage of compliant was more than 80%, with 20-80% was classified as partially compliant while less than 20% was non-compliant (Benner et al., 2002).

3.6.3 Anthropometric Parameters

Pertinent anthropometric parameter including Body Mass Index (BMI) of patients was assessed with details depicts as below:

(i) Height

The height of the patients was measured using SECA Body Tape Measure SE206. According to the National Health and Nutrition Examination Survey (NHANES), Anthropometry Procedures Manual which was published in 2009, participant was required to remove any hair ornaments, jewelry, buns, or braids from the top of the head. Then, the participant should stand up straight with the heels together touching the wall and toes apart. Participant should stand with body weight evenly distributed and both feet flat on the platform. Furthermore, it is important to make sure the back of the head, shoulder blades, buttock and heels are contacting the wall. Moreover, the head of the participant should aligned in Frankfort horizontal plane. Next, the headpiece was lowered done until it rest on top of the participant's head (compress the hair if necessary). Instruction to look straight, stand as tall as possible, take a deep breath and holding the position are given to the participant. The level of the was taken parallel to eye level and to the nearest 0.1cm.

(ii) Dry Weight

Dry weight of participant was obtained from the dialysis record books as secondary data.

(iii) Body Mass Index (BMI)

BMI of patients was computed based on patient's dry weight and height. The formula is weight (kg)/ height^2 (m). The data was recorded to the nearest 0.1 kg/m^2. BMI of patients was categorized into underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), Overweight (25.0- 29.9 kg/m^2) and Obese (≥30.0 kg/m^2) (MOH, 2005).

3.6.4 Biochemical Parameters

Serum albumin of patients was obtained from dialysis centres as secondary data from patient's medical history. According to medical nutritional therapy in 2005, the ideal range for serum albumin is >35-40 mg/dl and low serum albumin is <35-40 mg/dl.

3.6.5 Dietary Intake

Dietary intake of patients on dialysis day and non-dialysis day were obtained. For dialysis day, researcher performed a 24 hour dietary recall. On the other hand, for non-dialysis day, a food record was given to patients to fill up and it was clarified through telephone call. In order to obtain data on dietary intake of protein, phosphorus and dietary acid load, the food intake was analysed using Nutritionist Pro Software. There are two methods to measure for dietary acid load which are net acid production (NEAP) and potential renal acid load (PRAL). NEAP is the total amount of acid excreted while PRAL is the amount of acids and alkalis produced . Formula used to calculate NEAP and PRAL are shown below:

Net endogenous acid production (NEAP) (mEq/day) = (54.5 × protein [g/day]/potassium [mEq/day])- 10.2

(Frassetto et al., 1998).

PRAL (mEq/d) = 0.4888 × protein intake (g/day) + 0.0366 × phosphorus (mg/day) - 0.0205 × potassium (mg/ day) -0.0125 × calcium (mg/day) - 0.0263 × magnesium (mg/day)

(Remer & Manz, 1994)

Both methods can reflect long term dietary intake. The presence of physiological bases in PRAL and reflecting the estimation rate of intestinal absorption of some nutrients, ion balance of potassium, calcium, magnisum and phosphate dissociation at pH of 7.4 (Osuna-Padilla et al., 2019), justify the used of PRAL to estimate DAL of patients in this study. The data needed for calculation of PRAL was obtained from Nutritionist Pro analysis which include protein, phosphorus, potassium, calcium and magnesium intake.

3.6.6 Bone Quality

Bone quality was assessed by using Quantitative ultrasound (QUS) which is a convenient and popular tool to screen for osteoporosis. QUS transmits high frequency sound waves generated by the QUS device to examine the bone health. Based on several in vitro studies, QUS indices are significantly correlated with bone mineral density (BMD), a bone microarchitecture and mechanical parameters. QUS can differentiate subjects whether they have fracture history and also predict future fracture risk. The gold standard method recommended by the World Health Organization in the diagnosis of

osteoporosis is dual-X-ray absorptiometry (DEXA). However, QUS was chosen because it is more cheaper, portable, does not emit ionizing radiation and easy to perform compare to DEXA devices which are less accessible. Parameter generated by QUS is the speed of sound (SOS). SOS refers to the division of transmission time of the sound waves in meter per second (m/s) through length of body part investigated. Attenuation happens when sound waves travel through bone and soft tissue and the energy are absorbed. Radial part of skeleton was examined. Z-score indication for low bone quality is less than-2 while normal bone quality is >-2 (Du et al., 2015).

3.6.7 Serum phosphate level

An average value of three most recent serum phosphate was obtained from patients dialysis record books as secondary data. The recent of obtaining three value was to observe the trend of serum phosphate in the past 9 months, whether it is increased, maintained or reduced. Patients was considered non-adherent when the average of the pre-dialysis serum phosphate levels (past 3 months from data collection) exceeded 4.5 mg/dL according to Kidney Disease: Improving Global Outcomes (KDIGO) (2017). Based on Medical Nutritional Therapy (2005), the ideal serum phosphate level ranged from 0.8-1.6mmol/L, low serum phosphate was <0.8mmol/L and high serum phosphate was >1.6mmol/L. Serum phosphate help in predicting a greater reduction of eGFR where increase in 1mmol/L of serum phosphate was related to a 0.34 mL/min/month decline of eGFR with significant at p=0.02 (Chue et al., 2011).

3.7 Ethical Approval

Prior to the commencement of the study, ethical approval for the study protocol was obtained from the Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia (JKEUPM). Approval from hemodialysis centres was acquired prior to data collection.

3.8 **Pre-Testing**

A pre-testing was conducted in Hospital Serdang, Selangor. The pre-testing was carried out among 10 patients who met the inclusion and exclusion criteria. The purpose of pre-testing was to test the understanding of the participants on the questionnaire. Time taken to complete the questionnaire was recorded. The instruction and questions in the questionnaire were assessed in terms of clarity and simple to understand. Feedback given by the participants were took into consideration and appropriate amendment made accordingly. Patients taking part in pre-testing were excluded from the data collection sample later.

3.9 Procedures

Data collection was conducted from February to March 2020. First of all, prior to the commencement of the study, ethical approval was obtained from UPM's Ethics Committee for Research Involving Human Subjects (JKEUPM). Application letters was sent to selected dialysis centre and approval was gained before the data collection process begin. An information sheet contains relevant information pertaining to the study was distributed to all respondents. Written consent was obtained from participants before answering the questionnaire. During the dialysis session, participant answered the interviewer-administered questionnaire which include the social demographic, clinical data, and 24 hour diet recall. Ultrasound bone quality test was performed during the dialysis session.

3.10 Statistical Analysis

The IBM SPSS Statistics version 24 was used to analyse the data obtained. The significance level was set at $p< 0.05$. Data was checked for normality prior to further analysis. For normality testing, the data was considered normal if the skewness is between -2 and +2 while for Kolmogorov-Smirnov, the data is normality distributed if $p>0.05$. For univariate data, mean, standard deviation and normality testing were used to present the analysis of continuous data while frequencies and percentage were presented for categorical data. The dependent variable, serum phosphate level was a continuous variable. Thus, for bivariate analysis, associations between independent variables such as sociodemographic factor, clinical factors, nutritional status,dietary factors and bone quality were analysed using Pearson's Product Moment Correlation and Pearson Chi-Square Test. Continous normal data was analysed using Pearson's Product Moment Correlation while categorical data was analysed using Chi-Square Test.

CHAPTER FOUR

RESULTS AND DISCUSSIONS

4.1 Socio Demographic Characteristics

All the data for variables were normaly distributed. A total of 99 eligible patients were recruited. Table 5 shows the distribution of patients based on their sociodemographic characteristics. The mean age of the patients was 56.0 $\pm$ 11.0 years old with the youngest was 26 and the eldest was 78 years old. There were higher proportion of young adults (60.6%) than older adults (39.4%), was in line with national data from National Renal Registry (2016) where highest treatment rates found in categories of less than 65 years old. The distribution of sex was rather comparable was supported by study Leong et al. (2015), where the distribution of male and female undergoing dialysis remained constant for the past 10 years which is at 55% to 45% respectively. Most of the patients (73.7%) were Malay, followed by Chinese (22%), Indian (3.0%) and Others (1.0%). For educational level, most of the patients possessed secondary education (53.5%), followed by tertiary education (30.3%). There were 15.2% of patients completed primary education while 1.0% did not have any formal education. A majority of patients were married (86.9%), 12.1% were single and 1.0% were divorced. The unemployment rate was high , with approximately every 8 in 10 patients were not working. This scenario is worrying as more than 60% of the subjects are at the work productive age. High unemployment rate among dialysis patients is an universal issue with physical limitation, hemodialysis and work schedules conflict, low support rate from employers and family members advice were among the commonly reported factors (Huang et al., 2017).

Table 5: Distribution of Patients According to Socioddemographic Characteristics (*n* = 99)

Variable	n (%)	Mean ± SD	Range
Age (years)		56.0 ± 11.0	26 – 78
Less than 60 years old	60 (60.6)		
60 years old and above	39 (39.4)		
Sex			
Female	49 (49.5)		
Male	50 (50.5)		
Ethnicity			
Malay	73 (73.7)		
Chinese	22 (22.2)		
Indian	3 (3.0)		
Others	1 (1.0)		
Educational level			
No formal education	1 (1.0)		
Primary	15 (15.2)		
Secondary	53 (53.5)		
Tertiary	30 (30.3)		
Marital status			
Single	12 (12.1)		
Married	86 (86.9)		
Divorced	1 (1.0)		
Employment Status			
Working	18 (18.2)		
Not working	81 (81.8)		

4.2 Clinical Factors

Table 6 shows the distribution of patients based on their clinical factors including dialysis duration and medical compliance to phosphate binder. The mean duration of dialysis was 65.3 ± 53.8 months, varied widely from 6 to 264 months. Compliance on phosphate binder was satisfactory with a majority of subjects (74.7%) complied with the prescription, while a quarter of them complied partially. The finding is supported by Karamanidou et al. (2008) and Ghimire et al. (2015) which non-compliant to phosphate binder range from 22 to 74% and 13.9 to 98.6% respectively. In the best of knowledge, there is no standard measurement for adherence or specific definition for adherence level, thus contributing to the variation of compliance rate in previous study. None of the patients falled under the non-compliance category. The high compliance rate reported by subjects were contradict with (Arenas et al., 2010) which claim that hemodialysis patients showed higher nonadherence to the prescription. The reasons behind is due to they are in the category of chronic patients with absence of immediate discomfort or risk and their treatment might also requires lifestyle changes (Arenas et al., 2010).

Table 6: Distribution of Patients According to Clinical Factors (*n* = 99)

Variable	n (%)	Mean ± SD	Range
Clinical Factor			
Dialysis Duration (months)		65.29 ± 53.75	6-264
Phosphate binder compliance		1.26 ± 0.44	
Complied (>80%)	74 (74.7)		
100%	60 (60.6)		
80-100%	14 (14.1)		
Partially compliance (20-80%)	25 (25.3)		

Table 7 shows perceived factors that attribute to poor compliance on phosphate binders among the patients. Forgetfullness, high pill burden and the physical appearance of the phosphate binders eg the size were among the factors that hinder compliance among the patients. There findings concur with earlier studies (Arenas et al., 2010; Chan, Zalilah & Hii, 2012; Covic & Rastogi, 2013; Ghimire et al., 2015). Dialysis patients are likely to have high pill burden attributed to presence of multiple comorbidities (Parker et al., 2014). As poor medical adherence has been associated with increased mortality, poor quality of life and increased healthcare costs, appropriate (Kaveh & Kimmel, 2001; Cleemput et al., 2004; Esposito et al., 2009). Intervention and strategies should be initiated to reduce poor medical compliance among the patients.

Table 7: Distribution of Patients According to barriers in taking phosphate binder (*n* = 39)

Barriers*	**Number, n(%)**
Forgotten	33 (84.6）
Bad taste, tablets were too big, difficult to swallow, or chew.	9 (23.1)
High pill burden.	9 (23.1)
Feeling embarrassed or uncomfortable of taking medication when going out.	4 (10.3)
Unclear about the dosage and timing needed for phosphate binders.	2 (5.1)
Feeling unconfortable after taking.	1 (2.6)
Other reason(s)	2 (5.1)

* multiple responses are possible

4. 3 Nutritional status of Patients

Table 8 shows the distribution of patients based on their nutritional status. Mean BMI for patients was 25.70± 4.92 kg/m^2, ranged from 13.50 kg/m^2 to 39.76 kg/m^2. Mean BMI of patients were slightly higher than the national survellience data at 24.4 kg/m2 (National Renal Registry, 2016). Only approximately 40% of the patients had normal BMI with slightly more than 50% of the patients were either overweight or obese. There were another 4.0% of the patients were underweight. Despite higher BMI had been associated with better nutritional status and better survival among hemodialysis patients, a phenomenon known as reverse epidemiology (Kalantar-Zadeh et al., 2010; Kim et al., 2019), thus overly obese should be avoided. The mean dry weight and height of the patients were 67.39±16.03 kg and 161.27± 9.39 cm respectively. Mean of serum albumin was 39.02± 3.63 g/L. The mean value is comparable with National Renal Registry (2016) which was 38.0±4.9 g/L. On the other hand, there were high proportions of patients (89.9%) had ideal serum albumin while approximately 10% had low serum albumin level. The mean of the serum albumin level was 39.02± 3.63 As low serum albumin or hypoalbuminemia was strongly related with increase risk of mortality and morbidity among hemodialysis patients (Kinney, 2006), it is imperative to ensure appropriate albumin level among hemodialysis patients. On the other hand, it is noteworthy that albumin is a negative acute phase protein and hence has limited use in the assessment of nutritional status due to be affected by malnutrition and inflammatory reactions. Future studies should consider the use of pre-albumn as a more sensitive indicator to reflect nutritional status of dialysis patients.

Table 8: Distribution of Patients According to Nutritional Status (*n* = 99)

Variable	n (%)	Mean ± SD	Range
Body Mass Index (kg/m^2)		25.70± 4.92	13.50-39.76
Underweight (< 18.5)	4 (4.0)		
Normal (18.5-24.9)	43 (43.4)		
Overweight (25.0-29.9)	35 (35.4)		
Obese (≥30.0)	17 (17.2)		
Dry weight (kg)		67.39±16.03	33.50-121.00
Height (cm)		161.27± 9.39	131.00-185.40
Serum Albumin (g/L)		39.02± 3.63	21.51-44.33
Ideal (>35-40)	89 (89.9)		
Low (<35-40)	10 (10.1)		

4.4 Dietary Intakes of Patients

Table 9 shows the distribution of patients based on their dietary intake in terms of protein, phosphorus and acid load. Mean dietary protein intake was 47.57 ± 22.90 g/day, ranged from 8.52 to 110.12g. Inadequate intake of dietary protein was prevalent with close to 90% of the patients failed to achieve the recommended intake. Globally, despite the advances in the treatment hemodialysis patients, many still succumb to protein-energy wasting. Dietary restriction and poor appetite were among some of the factors that attribute to poor intake of dietary protein among dialysis patients (Mehrotra Rishishwar & Sharma, 2015).

For dietary phosphorus intake, the mean was 699.85± 347.70 mg with the lowest value was 121.63mg and the highest was 1446.08mg. Half (53.5%) of patients had low dietary phosphate intake which is less than 700 mg /day, 26.3% had normal intake (700-1000mg/day) and 20.2% had excessive intake (>1000mg/day). As phosphate is found in foods that rich in protein such as meats, eggs and dairy products, and even phosphate food additives (Benini et al., 2011), therefore low phosphate intake was in line with low

protein intake too. Furthermore, mean for dietary acid load calculated using PRAL was 26.00 ± 16.06 mEq/day. The lowest value was -5.775 mEq/day and the highest value was 70.34 mEq/day. To the best of knowledge, there were no published data for DAL among hemodialysis patients, making comparison with other studies not possible. Nevertheless, DAL of the patients was found to be higher than non-hemodialysis Japenese (Akter et al., 2017) and Swedish adults (Xu et al., 2016). PRAL in this study cohort also found to be higher than the CKD population in Washington (Ikizler et al., 2016) . Thus, comparing to non-local studies, the diet of patients in this study was acidic compare to non-hemodialysis adult and CKD population. As high dietary acid load score was associated with a higher risk of total mortality and mortality from CVD (Akter et al., 2017) and acknowledging CVD is one of the most important causes of death among dialysis population, more studies are warranted to delineate the possible association between DAL and health or mortality risk among dialysis patients.

Table 9: Distribution of Patients according to Dietary Intake (n=99)

Variable	**n (%)**	**Mean ± SD**	**Range**
Dietary Protein(g)		47.57± 22.90	8.52-110.12
Inadequate (<1.2g/kg BW)	87（87.9）		
Adequate (1.2-1.3g/kg BW)	4 （4.0）		
High (>1.3 g/kg BW)	8 （8.1）		
Dietary Phosphorus Intake (mg)		699.85± 347.70	121.63-1446.08
Low (<700 mg)	53 （53.5）		
Normal (700-1000mg)	26 （26.3）		
Excessive (>1000mg)	20 (20.2)		
Dietary Acid Load (DAL)mEq/day		26.00 ± 16.06	-5.775-70.34
mEq/kg/day		0.42± 0.31	-0.09-1.54

4.5 Bone Quality

Table 10 shows the distribution of patients according to bone quality. The mean z-score for bone quality was -2.01 $\pm$ 2.41 while the median was 1.00. The weightage for normal bone quality and the low bone quality is almost the same with more patients (53.5%) had z-score in the normal range while 46.5% had z-score in low bone quality range. This finding is in agreement with the prevalence of bone disorders in dialysis patients at the global level as reported to be between 33% and 67% (Sanusi et al., 2010). Bone disease is highly prevalent in patients with chronic kidney disease on dialysis, resulting form bone turnover abnormalities and the decrease of bone mineral density (Slouma et al., 2020). Bone and mineral metabolism malfunction usually seen in end-stage renal disease patients may lead to reduce bone quality and increased of fracture risk (Mirfakhraee et al., 2012), which signify appropriate interventions. It is however noteworthy that the bone quality of the patients was determined using quantitative ultrasound, which may not as accurate as the measurement of bone mineral density by gold standard, Dual energy x-ray absorptionmetry (DEXA). Future studies are required to employ more senstitive instrument in the determination of bone quality and bone quantity of hemodialysis patients. In addition, measurement of bone mineral density is not a common practice in the management of dialysis (Tariq & Sulaiman, 2020). In light of bone and mineral metabolism are common among dialysis patients, more work are needed to improve the understanding on the importance of bone measurement among dialysis patients.

Table 10: Distribution of Patients according to Bone Quality

Variable	n (%)	Median	Mean ± SD	Range
Z-score		1.00	-2.01 ± 2.41	-11.50-4.60
Normal Bone Quality	53 (53.5)			
Low Bone Quality	46 (46.5)			

4.6 Serum Phosphate Level among patients

Table 11 shows the distribution of patients according to serum phosphate level. The mean of value of serum phosphate was 1.79 ± 0.37 mmol/L and ranged from 0.82mmol/L to 2.83 mmol/L. The mean serum phosphate was higher than the data retrieved from National Renal Registry (2016) with the value of 1.6 mmol/L, indicating higher prevalence of hyperphosphatemia among the study's patients which deserves attention from all parties including family members and healthcare professionals.

A majority of patients (78.8%) had hyperphosphatemia, while only one in 5 subjects had normal serum phosphate elevel. The finding is comparable to the study by Nor Baizura et al. (2013) that more than half of the patients (58.6%) showed elevated serum phosphate. The high prevalence of hyperphosphatemia is alarming considering a majority of the patients was less than 60 years old. The high prevalence of hyperphosphatemia among hemodialysis patients could probably due to phosphorus retention as net intestinal absorption is greater than renal excretion or removal during dialysis treatment. Optimal control of phosphate balance depends on three major aspects namely compliance to phosphate binders, dietary phosphorus and dialysis. The complexity of the dietary regimen that causes greater difficulty for the hemodialysis patients to restrict the phophorus-rich food items that are commonly found in daily life may have contributed to this. On the other hand, despite there were only approximately

20% of the patients had excessive dietary phosphate intake, the extra-phosphate load attributed to the widely use of inorganic phosphorus as food additives was not assessed in this study. Future studies should consider assessment of inorganic phosphorus in dietary assessment.

Table 11: Distribution of Patients according to Serum Phosphate Level (n=99)

Variable	n (%)	Mean ± SD	Range
Serum Phosphate (mmol/L)		1.79 ± 0.37	0.82-2.83
Low	0 (0.00)		
Ideal	21 (21.2)		
High	78 (78.8)		

4.7 Hypothesis Testing

Associations between sociodemographic factors, clinical factors, nutritional status, dietary factors, bone quality and serum phosphate level

Ha1: There is significant association between sociodemographic factors and serum phosphate level among hemodialysis patients.

Table 12 shows the associations between sociodemographic factors and serum phosphate level. For continuous data, age was analysed using Pearson correlation test. Meanwhile, for categorical variables such as sex, ethnicity, educational level, marital status and employment status were analysed using Chi-square test to determine their relationship with serum phosphate level.

There was a moderate but statistically significant negative correlation between age and serum phosphate level ($r= -0.365$, $p< 0.001$), indicating the younger the age, the higher the serum phosphate level. This finding was supported by Baraz et al. (2010),

Youngmee & Evangelista (2010) , Ahrari et al. (2014), Garagarza et al. (2017) and local study by Koya (2019). On the other hand, inconsistencies in findings were reported in other studies (Chan et al., 2012; Collinson et al., 2014; Masyeni et al. (2020). Younger patients faced higher difficulities to comply with hemodialysis regimen and claimed that they are more physically healthy and less prevalent to other negative health consequences while elder patients were more conservative and more consistent lifestyle to comply to hemodialysis regimen explaining the correlation (Kutner, 2001; Clark-Cutaia et al., 2014; Ahrari et al., 2014). Furthermore, more advanced age tend to have lower eGFR and macro-anatomical structural changes with larger medullary capacity until middle age, decreased cortical volume, larger and extra numerous renal because of ageing process (Denic, Glassock & Rule, 2016). To tackle for the behavioural problem among younger patients, individualize interventions and counseling may needed.(Clark-Cutaia et al., 2014).

Besides, there was no significant correlation found between sex and serum phosphate (r = 0.089, p = 0.766). Similar finding were reported by Rambod et al. (2010) while Chan et al. (2012) and Kugler et al. (2005) found that men had higher serum phosphorus level than women. Women are more health conscious than men, therefore men are more likely to challenge the dietary restricitons. Based on Table 12, the percentage of male and female with high phosphate level was negligible, at which was similar to the study conducted by Mehrotra, Rishishwar & Sharma (2015) that hyperphosphatemia where present in dialysis patietns, regardless of sex.

There were no significant associations found between serum phosphate with ethnicity (r = 1.927, p = 0.165), marital status (r = 0.031, p = 1.00) or employment status (r = 3.227, p = 0.109). The finding was contradict with local study (Chan et al.,2012) and Lee & Molassiotis (2002) at which the authors reported working patients had lower

compliance to dietary restriction.Working patients tend to consume more outside foods which generally contains higher phosphate due to addition of preservatives and seasonings, lead to poor dietary phosphorus restriction. All in all, the differences in the demographic of the patients may have contributed to the discrepancies. There was significant correlation between educational level and serum phosphate (r=15.725, p = <0.001). The finding is supported by Baraz et al. (2010). Non-equal distribution of these varibles among patients, limited sample size or geographical difference may lead to the discrepancies across the studies. In general, the first alternative hypothesis was partially failed to be rejected.

Table 12: Associations between sociodemographic and serum phosphate level of the patients (n=99)

Variables	Serum Phosphate n (%)		χ^2	r-value	p-value
	Ideal	High			
Age				**-0.365**[a]	<0.001*
Sex			0.089[b]		0.766
Male	10 (47.6)	40 (51.3)			
Female	11 (52.4)	38(48.7)			
Ethnicity			1.927[b]		0.165
Malays	13 (61.9)	60 (76.9)			
Non-malays	8 (38.1)	18 (23.1)			
Educational Level			15.725[b]		<0.001*
No, Primary	9 (42.9)	7 (9.0)			
Secondary	10 (47.6)	43 (55.1)			
Tertiary	2 (9.5)	28 (35.9)			
Marital status			0.031[b]		1.000
Single, divorced	3 (14.3%)	10 (12.8)			
Married	18 (85.7)	68 (87.2)			
Employment Status			3.227[b]		0.109
Working	1 (4.8)	17 (21.8)			
Not Working	20 (95.2)	61 (78.2)			

[a]Pearson correlation

[b]Chi-square test

*Significant result, p<0.05

Ha2: There is significant association between clinical factors and serum phosphate level among hemodialysis patients.

As shown in table 13, there was no significant correlation between dialysis duration and serum phosphate (r = -0.036, p= 0.723). The finding was in line with Masyeni et al. (2020) but contradict to the local study by Chan et al. (2012) and Koya (2019) where patients dialysis for longer duration were prone to have hyperphosphatemia. Patients that just begin their treatment may received better social support and, thus higher compliance rate is expected (Lam, Twinn & Chan, 2010). In addition, a significant correlation was found between medical phosphate binder compliance with serum phosphate level (r = 5.929, p= 0.021). The finding was comparable to Arenas et al. (2010) and Wileman et al. (2015) but contradict to other studies (Chan, Zalilah & Hii, 2012; Chiu et al. (2009); Koya et al. (2009). Futhermore, more than half of the patients (69.2%) self reported adherence to phosphate binder but shown high serum phosphate. The rational behind might because of good control of serum phosphate not only depending on medical adherence but also related to other factors such as compliance to dietary restriction and adequate dialysis (Young et al., 2004; Young et al., 2005; Rodriguez-Benot et al., 2005). In addition, self-reports medical adherence have high specificity but low sensitivity as patients may likely overestimate their adherence. The sensitivity can be further enhance by using validated scales, improve in estimation techiques, facilitate recall in subjects, assess the right way to construct and decrease the bias in social desirability (Stirratt et al., 2015). To conclude, the second alternative hypothesis was partially failed to be rejected.

Table 13: Associations between clinical factors and serum phosphate level of the patients (n=99)

Variables	Serum Phosphate n (%) Ideal	High	χ^2	r-value	p-value
Dialysis Duration (months)				-0.036[a]	0.723
Medical Compliance			5.929[b]		0.021*
Adhered	20 (95.2)	54 (69.2)			
Partially adhered	1 (4.8)	24(30.8)			

[a]Pearson correlation

[b]Chi-square test

*Significant at p< 0.05

Ha3: There is significant association between nutritional status and serum phosphate level among hemodialysis patients.

As shown in Table 14 , there was no significant correlation between BMI and serum albumin with serum phosphate level, indicating no correlation of nutritional status with serum phosphate. The finding was in line with non-local study by Masyeni et al. (2020) but was contradicted to study by Garagarza et al. (2017) and Kim et al. (2017). Besides, hypophosphatemia was correlated with lower serum albumin but it lead to lower survival rate among the normal and hyperphosphatemia patients as low serum albumin lead to higher nutritional risk (Garagarza et al., 2017; Pourhassan et al., 2019; Kim et al., 2017). In addition, there was no significant correlation found between dry weight and height with serum phosphate level.

In this study cohort, majority of the patients had ideal serum albumin level, hence no significant relationship was found. Further study is needed to determine the association between serum albumin and serum phosphate. The third alternative hypothesis was rejected.

Table 14: Associations between nutritional status and serum phosphate level of the patients (n=99)

Variables	r-value	p-value
BMI (kg/m$^{2)}$	0.110	0.280
Dry Weight (kg)	0.177	0.080
Height (cm)	0.149	0.141
Serum Albumin (g/L)	0.121	0.231

Ha4: There is significant association between dietary intake of protein, phosphorus, acid load and serum phosphate level among hemodialysis patients.

Table 15 shows the associations between dietary intake of protein, phosphorus, acid load with serum phosphate level. There were no significant associations between dietary protein, dietary phosphate and acid load with serum phosphate level. The finding for dietary protein was not in agreement with previous study by Shinaberger et al. (2008) and Mart et al. (2001). The finding for phosphorus intake was contradicted with Chan et al. (2012) and Gutiérrez, Isakova, Enfield, & Wolf (2011). There might be under or over reporting regarding their dietary intake that affect the data on dietary protein and phosphate intake. The use of two-day dietary data on the other hand may not be sufficient

to reflect the habitual dietary intakes of subjects. Future studies should consider food frequency questionnaire or the employment of long term dietary data.

In addition, the data taken did not focus on the phosphorus intake in inorganic food sources including phosphorus additives which are commonly found nowadays to extend shelf-life, enhance flavor and colour and retain the moisture of foods. Some of the processed food contains phosphorus additives and cola drinks contribute significantly to dietary phosphorus. However, it is not easy to be counted as phosphate additives as less available in the nutrient databases and food compositions tables (Benini et al., 2011; Cupisti et al., 2012) which may cause the inaccuracy of the data. For dietary acid load, the finding was in contrast with study by Khairallah et al. (2017) which shown the higher the DAL, the higher the serum phosphate. High anion gap (AG) metabolic acidosis occured with severe hyperphosphatemia as a result from dietary phosphate consumption (Sadjadi & Pi, 2017). However, severe hyperphosphatemia is not usually related to metabolic acidosis due to wide gap in the field (Seifter, 2014) where metabolic acidosis should be listed as one of the causes of hyperphosphatemia. DAL calculation was also depending on dietary protein and dietary phosphate intake which may lead to inaccuracy of the result obtained. More study related to the relationship between DAL and serum phosphate is needed so that metabolic acidosis among hemodialysis patient can be controlled and reduces the mortality rate. The forth alternative hypothesis was rejected.

Table 15: Associations between dietary intake of protein, phosphorus, acid load and serum phosphate level of the patients (n=99)

Variables	r-value	p-value
Dietary Protein (g)	-0.026	0.798
Dietary Phosphate (mg)	-0.122	0.228
Dietary Acid Load (DAL)mEq/ day	-0.076	0.456

Ha5: There is significant association between bone quality and serum phosphate level among hemodialysis patients.

Table 16 shows the relationship between bone quality and serum phosphate. There was no association found between z-score and bone speed of sound (SOS) value with serum phosphate. The finding was contradicted with Campos-Obando et al. (2017) and Block et al. (2004) who found higher serum phosphate was related to higher fracture risk. Inability to remove phosphate from the body increases the risk of mineral and bone disease, which related to osteoporosis and fracture (Umeukeje , Mixon & Cavanaugh, 2018).

For this study cohort, non-detectable bone and missing data may contributed to the inaccurate result. Therefore, in order to obtain more accurate result, bone density analysis via X-ray absorptiometry or bone densitometry which is the gold standard tool for bone mass and fracture risk assessment should be considered in future studies. The fifth alternative hypothesis was rejected.

Table 16: Associations between bone quality and serum phosphate level of the patients (n=99)

	Serum Phosphate n (%)		χ^2	r-value	p-value
Variables	**Ideal**	**High**			
z-score			**0.375[b]**		0.540
<-2	10 (47.6)	43 (55.1)			
>-2	11 (52.4)	35 (44.9)			
SOS				0.035[a]	0.734

SOS : speed of sound

[a]Pearson correlation

[b]Chi-square test

CHAPTER 5 CONCLUSION, STRENGTHS, LIMITATIONS AND RECOMMENDATIONS

5.1 Conclusion

In conclusion, hyperphosphatemia was prevalent among hemodialysis patients, which warrant attentions from relevant authorities. There were significant associations between sociodemographic factors (age, educational level) and clinical factor (compliance to phosphate binder). Therefore, healthcare professional including dietitians should be sensitive with the compliance of young patients. A close monitoring on the compliance on phosphate binder is imperative. Inversely, nutritional status, dietary factors and bone quality were found no associations with serum phosphate levels which were congruent with previous studies done. Moreover, the results of this study also draw the attention on high educational level did not ensure better knowledge on how to control serum phosphate level. Thus, healthcare professional or dietitians should play the roles to provide education and individual counselling to identify the factors behind and effective intervention can be done. At the same time, it is crucial to increase the awareness among hemodialysis patients such as the consequences of hyperphosphatemia and improve on the non-compliance to treatment regimen. For barriers in taking phosphate binder, intervention need to be planned to tackle on the forgotten, bad taste, tablets were too big, difficult to swallow, or chew and high pill burden. For example, patients can discuss with prescriber on how to reduce the number of pill but maintaining the dose required. Nearly half of the patients had low bone quality. Although this study unable to confirm on the association between serum phosphate level and bone quality which is the fracture risk, it warrants for further studies to prevent the comorbidities of CKD. Despite no significant associations were found between serum

phosphate levels and dietary acid load or bone quality, the high prevalence of poor bone quality and high DAL among the HD patients demand for more studies in the future on these relatively under-studied aspects.

A majority of patients had normal body mass index and serum albumin that may indicate better nutritional status. It is important to maintain good nutritional status as poor nutritional status lead to higher comorbidities and mortality among hemodialysis patients. For dietary intake, the inadequate amount of protein acquires attention from dietitian as poor dietary intakes will contribute to poor nutritional status while patients might purposely avoid high protein food which is also rich in phosphorus that will cause high serum phosphate level. Measures can be taken such as nutritional education on the ways to choose food wisely as well as removal of phosphate from vegetables by cutting in smaller piece and soaking in water to rinse away some phosphate content in vegetables.

5.2 Strengths

Data was collected through interviewer-administrated questionnaire which was face-to-face. It helped to reduce data bias and provide better understanding on the questions. This study investigated on the bone quality that related to fracture risk and dietary acid load that related to metabolic acidosis among hemodialysis patients which were much challenging and yet limited study to support on the association. Thus, the finding of this study can provide baseline data future research. Last but not least, health care professionals can get better understanding on the factors affecting serum phosphate level and provide better and individualised interventions to improved on the medical compliance rate.

5.3 Limitations

Due to pandemic of covid-19 disease, the number of patient targeted was not achieved with 70.6% of overall response rate obtained. The study was completed in three dialysis centres in the area of cheras and bangi, which might not be able to represent the population in the state. Besides, dietary recall bias might occurred because of under-reporting their dietary intake. Two-days diet recall might not able to represent their typical diet pattern. Proper training for emunerator is needed for better diet recall skills. Increasing the number of days of dietary recall to three days diet recall or food frequency questionnaire can increase the accuracy of diet recall. On the other hand, as dietary intake measurement is often self-reported, which have inherent limitations, the use of biomarkers which capable of objectively assessing food consumption should be considered in future studies. Furthermore, bone quality of the patients was determined using quantitative ultrasound, which may not as accurate as the measurement of bone mineral density by gold standard, Dual energy x-ray absorptionmetry (DEXA). Serum albumin level was possible affected by malnutrition and inflammatory reaction which lead to inaccuracy of the reading. In addition, interviewer-administered questionnaire provides answer that highly depending on honesty of the patients as well as the technique of interviewer's skills in probing patients to answer as close to their real situation as possible.

5.4 Recommendations

Larger sample size and wider area of study should be conducted to confirm on the finding of the study. For dietary recall bias, well-practiced technique is important and household measures can be used to help patient in recalling and avoid under or over-

reporting. For better represent of their usual dietary intakes, food frequency questionnaire (FFQ) or the employment of long term dietary data can be used. To access on higher accuracy regarding bone mineral density, the gold standard, Dual energy x-ray absorptionmetry (DEXA) is recommended. Pre-albumin, a more sensitive indicator to reflect nutritional status of dialysis patients can be used instead of serum albumin. Last but not least, health care professional should be more supportive and understanding when trying to intervent on the non-compliance of treatment. Support and encouragement by family and friends also important to build confidence for patients to overcome the difficulties and barriers. Dietitians can play their role in providing nutrition education in more creative way and easier to understand. Simple but user friendly pamplets can be given as a take-home messages and family members should remind patients when they are showing non-compliance. Regular assessment on dietary, biochemical data and nutritional status should be performed to improve on patient's quality of life and reduce comorbidities.

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APPENDIX A ETHICAL CLEARANCE

Ref. No: UPM/TNCPI/RMC/JKEUPM/1.4.18.2 (JKEUPM)
Date: 2 June 2020

Dear Prof./Dr./Mr./Ms.,

APPLICATION FOR JKEUPM ETHICAL CLEARANCE: APPROVED

With reference to the above, I am pleased to inform you that your application for ethical clearance for the research project entitled '**Associations between Sociodemographic, Clinical Factor, Nutritional Status, Dietary Factors, Medical Factor, Bone Quality and Serum Phosphate Level among Haemodialysis Patients.**' has been approved.

Please note that the official letter of approval will be issued as soon as possible. However, the ethical clearance is considered effective from the date of this email, and you may now proceed with your research.

Kindly remind the ethical approval is required in the case of amendments/ changes to the study documents/ study sites/ study team.

Researchers should also complete a Study Final Report upon study completion. The form can be obtained from the Ethics Committee for Research Involving Human Subjects (JKEUPM) website (http://www.tncpi.upm.edu.my/faildokumen).

If you have any enquiries, please contact Ms. Nurulhasanah Ishak (03-97691605) or Ms. Nor Ellia Abd Ajis (03-97691244).

Note: Please use this reference number for any transaction.

- **JKEUPM-2020-115**

Thank you.

Yours faithfully,

Prof. Dr. Zamberi Sekawi
Chair
Ethics Committee for Research Involving Human Subjects
Universiti Putra Malaysia

APPENDIX C RESPONDENT'S INFORMATION SHEET AND CONSENT

ENGLISH VERSION

JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN MELIBATKAN MANUSIA (JKEUPM)
UNIVERSITI PUTRA MALAYSIA, 43400 UPM SERDANG,
SELANGOR, MALAYSIA

FORM 2.4:
RESPONDENT'S
INFORMATION SHEET AND INFORMED CONSENT FORM

Please read the following information carefully and do not hesitate to discuss any questions you may have with the researcher.

1. STUDY TITLE :

Associations between sociodemographic, clinical factors, nutritional status, dietary factors and bone quality with serum phosphate level among hemodialysis patients.

2. INTRODUCTION:

Hyperphosphatemia is common among hemodialysis patients which are often associated with increased morbidity and mortality among them. Despite hyperphosphatemia is a common global phenomena among hemodialysis patients, there are dearth of information on this among hemodialysis patients in Malaysia. Studies on how clinical factors, nutritional status, dietary factors, and bone quality may be associated with serum phosphate level are lacking in the local context.. Thus, this study aims to determine whether are there associations between sociodemographic, clinical factor, nutritional status, dietary factors, medical factor and bone quality with serum phosphate level among hemodialysis patients in Malaysia. The study involved 143 respondents. The study duration for each respondent is approximately one hour.

3. WHAT WILL YOU HAVE TO DO?

Respondent will be interviewed by the researcher and guided by the researcher to complete a pre-tested structured questionnaire to obtain information on socio demographic and medical adherence. Following the completion of the questionnaire, the respondent will be interviewed by the researcher to obtain a dietary recall on non-dialysis day. Respondent will then be provided with a dietary record form to be filled for food intake on dialysis day. For subjects who are illiterate, a telephone interview will be performed. For bone quality, researcher will perform bone quality test on subjects using Omnisense sunlight device. Information on serum phosphate level, anthropometry data and biochemical data will be obtained from subjects' medical record book.

4. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

Hemodialysis patients who are non-Malaysians and with dementia and mental illness will be excluded from the study. Besides, hemodialysis patients who were hospitalized in previous three months, diagnosed with severe heart or lung failure with unstable vital signs, with physical disabilities and acute or chronic hepatitis B and C will be excluded from the study. This is a voluntary study in which the respondents have the right to withdraw from the study anytime if they feel uncomfortable with the research procedures.

5. WHAT WILL BE THE BENEFITS OF THE STUDY:

(a) TO YOU AS THE SUBJECT?

You will be able to know your nutritional status, dietary intake, medical adherence, bone quality and control of serum phosphate level. A small gift will be given as a token of appreciation.

(b) TO THE INVESTIGATOR?

Information obtained can be used by researchers and healthcare professionals to plan for intervention programs to improve hyperphosphatemia among hemodialsysis patients.

6. WHAT ARE THE POSSIBLE RISKS?

There are no possible risks in this study as respondents as there are no invasive techniques involved.

7. WILL THE INFORMATION THAT YOU PROVIDE AND YOUR IDENTITY REMAIN CONFIDENTIAL?

Yes.

8. WHO SHOULD YOU CONTACT IF YOU HAVE ADDITIONAL QUESTIONS DURING THE COURSE OF THE RESEARCH?

Ethics Committee for Research Involving Human Subject UPM (JKEUPM) Review Panel has approved the study, and may be reached through the following address for information regarding rights of study participants, including grievances and complaints.

Ethics Committee for Research Involving Human Subject UPM (JKEUPM)
Research Management Centre
Office of The Deputy Vice Chancellor (Research & Innovation)
University Putra Malaysia
43400 UPM Serdang, Selangor

Should you have any inquiry about the study, please contact with the researcher of this study Ms. Ng Pee Chien, at 019-5228673 (email: alicia.ng801@gmail.com) or supervisor of the study, Associate Professor Dr. Chan Yoke Mun at 03-97692433 (email: cym@upm.edu.my)

*Please initial here if you have read and understood the contents of this page*_____

9. CONSENT

I …… Identity Card No. …… address…… ……... ……..hereby voluntarily agree to take part in the research stated above *(clinical /drug trial/video recording/ focus group/interview-

based/ questionnaire-based).

I have been informed about the nature of the research in terms of methodology, possible adverse effects and complications (as written in the Respondent's Information Sheet). I understand that I have the right to withdraw from this research at any time without giving any reason whatsoever. I also understand that this study is confidential and all information provided with regard to my identity will remain private and confidential.

I* wish / do not wish to know the results related to my participation in the research

I agree/do not agree that the images/photos/video recordings/voice recordings related to me be used in any form of publication or presentation (if applicable)

* delete where necessary

Signature ……..…… Signature ……..…….

(Respondent) (Witness)

Date :…….. Name :……..

I/C No. :……..…..

I confirm that I have explained to the respondent the nature and purpose of the above-mentioned research.

Date ……..…… Signature ……..…….

MALAY VERSION

JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN MELIBATKAN MANUSIA (JKEUPM)
UNIVERSITI PUTRA MALAYSIA, 43400 UPM SERDANG,
SELANGOR, MALAYSIA

BORANG 2.4: PENERANGAN DAN PERSETUJUAN RESPONDEN

Sila baca maklumat berikut dengan teliti. Sekiranya anda mempunyai sebarang pertanyaan, sila kemukakan kepada penyelidik.

1. TAJUK KAJIAN

Hubungan antara sosiodemografik, faktor clinical, status nutrisi, faktor permakanan dan qualiti tulang dengan serum fosfat dalam kalangan pesakit hemodialisis di pusat dialisi tertentu.

2. PENGENALAN

Hyperphosphataemia adalah biasa dalam pesakit hemodialisis, yang sering dikaitkan dengan peningkatan morbiditi dan kematian. Walaupun hyperphosphataemia adalah fenomena global yang meluas dalam pesakit hemodialisis, terdapat kekurangan maklumat mengenainya di Malaysia. Kajian tentang bagaimana faktor klinikal, status pemakanan, faktor pemakanan dan kualiti tulang yang berkaitan dengan tahap serum fosfat kurang dalam konteks setempat. Tujuan kajian ini adalah untuk menentukan sama ada terdapat kaitan antara faktor sosiodemografi, faktor klinikal, status pemakanan, faktor pemakanan, faktor perubatan dan kualiti tulang dengan tahap serum fosfat dalam pesakit hemodialisis di Malaysia. Kajian ini melibatkan 143 orang responden. Setiap responden akan terlibat dalam kajian untuk masa lebih kurang satu jam.

2. APAKAH YANG PERLU ANDA LAKUKAN?

Responden akan ditemuduga oleh penyelidik dan dipandu oleh penyelidik untuk menyelesaikan soal selidik berstruktur yang telah diuji terlebih dahulu untuk mendapatkan maklumat tentang pematuhan demografi sosial dan perubatan. Berikutan selesainya, responden akan ditemubual oleh penyelidik untuk mendapatkan penarikan diet pada hari tidak dialisis. Responden akan diberikan borang rekod pemakanan untuk diisi untuk pengambilan makanan pada hari dialisis. Bagi subjek yang buta huruf, temuduga telefon akan dilakukan. Untuk kualiti tulang, penyelidik akan melakukan ujian kualiti tulang pada subjek menggunakan peranti Omnisense. Data untuk tahap serum fosfat, data antropometri dan data biokimia akan diperolehi dari buku rekod perubatan.

4. SIAPA YANG TIDAK BOLEH MENYERTAI KAJIAN INI?

Pesakit hemodialisis yang bukan rakyat Malaysia dan dengan demensia dan penyakit menta akan dikecualikan daripada kajian ini. Selain itu, pesakit hemodialisis yang dimasukkan k hospital dalam tiga bulan sebelumnya, didiagnosis dengan kegagalan jantung atau paru-par dengan tanda-tanda vital yang tidak stabil, dengan ketidakupayaan fizikal dan hepatitis B da C yang akut atau kronik akan dikecualikan daripada kajian ini. Ini adalah kajian sukarela d mana responden mempunyai hak untuk menarik diri dari kajian pada bila-bila masa jika mereka merasa tidak selesa dengan prosedur penyelidikan.

5. APAKAH FAEDAH MENYERTAI KAJIAN INI?

a) KEPADA ANDA SEBAGAI PESERTA?

Anda akan dapat mengetahui status pemakanan anda, pengambilan makanan, pematuhan perubatan, kualiti tulang dan kawalan tahap serum fosfat. Hadiah kecil akan diberikan sebagai tanda penghargaan.

b) KEPADA PENYELIDIK?

Maklumat yang diperolehi boleh digunakan oleh penyelidik dan profesional penjagaan kesihatan untuk merancang program intervensi untuk mengurangkan hiperfosfatemia d kalangan pesakit hemodialisis.

6. ADAKAH IA BERISIKO?

Tidak ada risiko dalam kajian ini sebagai responden kerana tiada teknik invasif yang terlibat

7. ADAKAH MAKLUMAT DAN IDENTITI SAYA KEKAL RAHSIA?

Ya.

8. SIAPA YANG SAYA PERLU HUBUNGI SEKIRANYA SAYA MEMPUNYAI SOALAN TAMBAHAN SEMASA MENGIKUTI PENYELIDIKAN INI?

Panel Kajian JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN MELIBATKAN MANUSIA (JKEUPM) telah meluluskan kajian ini, dan boleh dicapai melalui alamat berikut untuk maklumat mengenai hak peserta kajian, termasuk keluhan dan aduan.

JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN MELIBATKAN MANUSIA (JKEUPM)

Pusat Pengurusan Penyelidikan

Pejabat Timbalan Naib Canselor (Penyelidikan & Inovasi)

Universiti Putra Malaysia

43400 UPM Serdang, Selangor

Sekiranya anda mempunyai sebarang pertanyaan mengenai kajian ini, sila hubungi penyelidik kajian ini, Cik Ng Pee Chien, di 019-5228673 (e-mel: alicia.ng801@gmail.com) atau penyelia kajian, Profesor Madya Dr. Chan Yoke Mun di 03-97692433 (e-mel:

cym@upm.edu.my)

Sila tandatangan di sini sekiranya anda telah membaca dan memahami kandungan halaman ini _____

9. PERSETUJUAN

Saya…… No Kad Pengenalan. ……

beralamat……

……..dengan ini bersetuju untuk mengambil bahagian secara sukarela dalam penyelidikan yang tersebut di atas *(kajian klinikal/percubaan ubat-ubatan/rakaman video/kumpulan sasaran/temuduga/ soal selidik).

Saya telah diberi penjelasan secara menyeluruh mengenai penyelidikan ini dari segi metodologi, risiko dan komplikasi (seperti tertulis pada Helaian Penerangan Responden). Saya memahami bahawa saya berhak menarik diri dari penyelidikan ini pada bila-bila masa tanpa memberi sebarang alasan.Saya juga memahami bahawa sebarang maklumat yang berkaitan identiti saya akan dirahsiakan.

Saya* berminat / tidak berminat untuk mengetahui keputusan kajian yang melibatkan saya.

I setuju/tidak bersetuju untuk imei/gambar/rakaman video/ rakaman suara digunakan dalam apa jua bentuk penerbitan atau pembentangan. (sekiranya berkaitan).

*potong yang tidak berkenaan

Tandatangan ……..…… Tandatangan ……..……

(*Responden*) (*Saksi*)

Tarikh :……. Nama :…….

No. K/P: ……

Saya mengesahkan bahawa saya telah menerangkan kepada responden ini sifat dan tujuan penyelidikan yang tersebut di atas.

Tarikh ……..…… Tandatangan ……..…….

APPENDIX D QUESTIONNAIRE

FACULTY OF MEDICINE AND HEALTH SCIENCES

DEPARTMENT OF NUTRITION AND DIETETICS

Questionnaire Form

Research Title:

ASSOCIATIONS BETWEEN SOCIODEMOGRAPHIC, CLINICAL FACTORS NUTRITIONAL STATUS, DIETARY FACTORS AND BONE QUALITY WITH SERUM PHOSPHATE LEVEL AMONG HEMODIALYSIS PATIENTS IN SELECTED DIALYSIS CENTRE.

Hubungan antara sosiodemografik, factor klinikal, status nutrisi, faktor permakanan dan qualiti tulang dengan serum fosfat dalam kalangan pesakit hemodialisis di pusat dialisi tertentu.

Researcher's Name: Ng Pee Chien

Matric Number : 193300

Supervisor's Name: Professor Chan Yoke Mun

Date:

Confidential and for research purpose only
Sulit dan untuk kegunaan kajian sahaja

Instruction:

This study is conducted for academic purpose. All information will be kept private and confidential. Thank you for your cooperation in answering this questionnaire.

Arahan: Kajian ini dijalankan untuk kegunaan akademik sahaja. Semua maklumat dalam kajian ini akan disimpan secara sulit. Terima kasih kerana menjawab borang ini.

SECTION A

1. Age / *Umur* : _____ years old / *tahun*
2. Date of Birth / *Tarikh lahir*: _____ (dd/mm/yyyy)
3. Sex / *Jantina*:

   ( ) Male / *Lelaki*

   ( ) Female / *Perempuan*
4. Ethnicity / *Bangsa*:

   ( ) Malay */ Melayu*

   ( ) Chinese / *Cina*

   ( ) Indian / *India*

   ( ) Others, please specify / *Lain-lain, sila nyatakan*: _____
5. Marital Status / *Status Perkahwinan*:

   ( ) Single / *Bujang*

   ( ) Married / *Berkahwin*

   ( ) Divorce / Berc*erai*
6. Educational Level / *Latar belakang pendidikan*:

   ( ) No formal education / *Tiada Pendidikan Formal*

   ( ) Primary Education / *Sekolah Rendah*

   ( ) Secondary Education / *Sekolah Menengah*

   ( ) Tertiary (Diploma/ Degree/ Master/ PhD) / *Pendidikan IPTA, Diploma ke atas*

   ( ) others, please specify / *Lain-lain, sila nyatakan* _____
7. Are you working currently / *Adakah anda bekerja sekarang*?

   ( ) Yes / *Ya*

( ) No / *Tidak*

8. Occupation / *Pekerjaan*: _____ (Part Time */ Sambilan*) (Full Time */ Sepenuh masa*)

9. Monthly personal income / *Pendapatan bulanan peribadi* : RM_____

10. Monthly household income / *Pendapatan bulanan isi rumah*: RM_____

11. How long had you been on hemodialysis / *Berapa lamakah anda telah menerima rawatan hemodialysis*? _____ month(s)/year(s) / *bulan/tahun*

12. What is the dosage for your phosphate binder? _____ mg

13. Do you comply with the phosphate binder prescription by doctor? / *Adakah anda mengambil ubat mengawal fosfat mengikut preskripsi doctor?*

( ) Yes / *Ya*

( ) No / *Tidak*

14. If not, how many times in the past week (7 days) you skip your phosphate binder? / *Kalau tidak, berapa kali anda tidak mengambil ubat untuk seminggu (7 hari) yang lepas?*

_____

15. May I know what are your barriers in taking the phosphate binders?

( ) Forgotten to take?

( ) Don't know how much or when to take it?

( ) Feeling embarrassed or uncomfortable of taking medication when going out?

( ) Feel uncomfortable after taking? Eg. stomach upset, diarrhea, constipation

( ) Bad taste, tablets were too big, difficult to swallow, or chew

( ) The doses are too much causing hard to comply.

( ) Other reason _____

SECTION B
Researcher will take the following data from your medical record.

Penyelidik akan mengambil maklumat berikut dari rekod perubatan anda.

1. Dry weight/ *berat badan* = _____ kg

Height/ *Ketinggian*= _____ cm

2. Serum albumin level _____ g/dL

3. Serum phosphate level (3 latest readings)

Paras serum fosfat _____ mg/dL

SECTION C

Dietary intake

Pengambilan Dietari

Information on dietary intake is collected for non-dialysis day and dialysis day.

Informasi tentang pengambilan dietary akan diambil untuk hari menjalani dialisis dan hari tidak menjalani dialisis.

Researcher will performed a 24-hour food recall for non-dialysis day and one-day food record will be given to subject for dialysis day.For subjects who are illiterate, a telephone interview will be performed.

Penyelidik akan merekodkan pengambilan makanan subjek untuk hari tidak menjalani dialisis dan rekod pemakanan satu hari akan diberikan kepada subjek untuk merekodkan pengambilan makanan hari menjalani dialysis. Untuk subjek yang buta huruf, penyelidik akan menelefon subjek untuk pengambilan dietari untuk hari menjalani dialysis.

Food Intake on Dialysis Day

Pengambilan Makanan untuk Hari Menjalankan Dialisis

Meal time *Waktu makan*	**Food/drink items** *Makanan/minimum*	**Amount** *kuantiti*	**Method of food preparation** *Cara masakan*

Food intake on Non-Dialysis Day

Pengambilan Makanan untuk Hari Menjalankan Dialisis

Meal time *Waktu makan*	**Food/drink items** *Makanan/minimum*	**Amount** *kuantiti*	**Method of food preparation** *Cara masakan*

SECTION D
Bone quality
Kualiti tulang

Quantitative ultrasound (QUS) value=

Nilai QUS =

**** THE END ****
**** *TAMAT* ****

Thank you for answering this questionnaire.
Terima kasih kerana menjawab soal selidik ini.