CORRELATION BETWEEN PHOSPHATE LEVEL AND PERITONEAL EQUILIBRATION TEST (PET) CHARACTERISTICS AMONG CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD) PATIENTS

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ABSTRACT

Hyperphosphatemia is the key abnormality that sets off a cascade of metabolic events in chronic kidney disease (CKD). End stage renal disease (ESRD) patients that undergo Continuous Ambulatory Peritoneal Dialysis (CAPD) uses the peritoneal membrane for solutes filtration and clearance. The differences on the evaluation of peritoneal membrane transport status can affect the rate of toxin removal – serum phosphorus, from the systems. The present study aimed to determine the prevalence of CAPD patients presented with high phosphate level after starting the treatment, to identify the risk factors associated with hyperphosphatemia and to find the significant correlation between the phosphate level and the PET characteristics. A retrospective study was applied for this research where the medical records of patients were reviewed and analyzed between January 2011 to December 2016. Data were collected successfully from 74 adult CAPD patients (41 male, 55.4% and 33 females, 44.6%), with mean age of 51.34 ± 13.75 year-old. In this study, Malays (n= 65, 87.8%) are the largest subjects recruited, while Chinese (n= 6, 8.1%) and Indians (n= 3, 4.1%) made the rest of the subjects. PET characteristics of CAPD patients showed 11 patients had high characteristic (14.9%), 24 high average (32.4%), 26 low average (35.1%) and 5 low (6.8%). There were 37 CAPD patients (50%) presented with high phosphate level after starting the treatment. Simple linear regression revealed that age (p = 0.0052), serum calcium (p = 0.0090), serum albumin (p = 0.0244), normalized protein catabolic rate (nPCR) (p = 0.0126), intact parathyroid hormone (iPTH) (p = 0.0012), total creatinine clearance (p = 0.0470), residual renal creatinine clearance (p = 0.390) and 24-hours urine volume output (p = 0.0060) were risk factors associated with hyperphosphatemia. Pearson's correlation analysis showed there was no significant correlation between phosphate level and PET characteristics (r = -.232, p = 0.070) while there was significant correlation between PET characteristics and peritoneal solute clearance (r = 0.4748, p < 0.001). In conclusion, serum phosphate level may be associated with daily dietary intake, metabolism and dialysis adequacy. There was no correlation between serum phosphate level and PET characteristic suggesting the rate of the toxin removal might not been affected by the differences on peritoneal membrane characteristics suggesting a further understanding on transport status in terms of its mechanism of toxin removal.

KEYWORDS: CAPD, serum phosphate level, hyperphosphatemia, PET characteristics, solute clearance.

INTRODUCTION

The first introduction of continuous ambulatory peritoneal dialysis (CAPD) was published in *Annals of Internal Medicine* by Robert Popovich and his colleagues in 1978 that explained their understanding with the new technique and it has been proven to be an alternatives for hemodialysis as well as intermittent peritoneal dialysis for treating uremic syndrome (Oreopoulos & Thodis, 2010). CAPD follows the rule of osmotic pressure (osmotic gradient) and ultrafiltration where solutes and water will move across the semipermeable membrane that can be described as movement from blood to dialysate or/and from dialysate to blood according to concentration gradients.

The physiology of peritoneal membrane influence mass transport during peritoneal dialysis, thereby affecting its therapeutic efficacy. The membrane is lined by mesothelium cells that produced thin layer of peritoneal fluid. Under the mesothelium layer there is a gel-like interstitial containing the connective tissue, capillaries and lymphatic (Lokesh & Arunkumar, 2013). The effective peritoneal surface area is critical for dialysis and it depends on the vascularity of the peritoneum as well as its surface area (Daugirdas, Blake, & Ing, 2007). It is to be note that the peritoneal cavity is different between every patient and within a patient under different conditions. The rate and extend of the solute transport basically, determined by the proximity of capillaries to the peritoneal surface and the difference in characteristic of peritoneal transport among different patients.

Thus, a systematic equilibration test is developed to evaluate the peritoneal membrane transport rates called Peritoneal Equilibration Transport (PET) which is first introduced by Zbylut J.Twardowski in 1987. The PET results allow the patients to be classified into high transporter (H), low transporter (L), high average transporter (HA) and low average transporter (LA) according to the solutes clearance rate (Twardowski et al., 1987). The status of peritoneal transporter influenced the rate of solute clearance in a way that it is parallel with the membrane effectiveness for ultrafiltration. The adequacy of ultrafiltration for waste product is crucial in chronic kidney disease (CKD) patients.

Phosphate is one of many waste products where the accumulation level becoming concern to the nephrologist and health professionals. Phosphate overload have become known and has been successfully analyzed to have association to the progression of CKD, left ventricular hypertrophy and vascular calcification particularly coronary artery calcification that eventually contribute to increase rate of mortality. Concern regarding development of CKD-MBD begin to appear even in early stages of CKD as in long term it eventually contribute to the pathogenesis of renal osteodystrophy particularly femur fracture. In CKD, hyperphosphatemia depict a signal that mineralization occur in order to compensate for the failure phosphate storage function in the skeleton.

Accumulated phosphate can only be removed though dialysis but differences in the thickness of peritoneal cavity may be the limitation. However, much uncertainty still exists

about the relation between PET status and the solutes removal. Due to this concern, study is done to correlate the differences in the transporter status (H, HA, L, LA) towards the effectiveness of phosphate removal from the body. The prevalence of CAPD patients presented with high phosphate level after starting the treatment is determine as well. In addition, the predictors that could possibly contribute to the increase of phosphate level among CAPD patients in HTAA is determine to assist the nephrologists as debate continues about the best strategies for the management of ESRD patients.

METHODS

Study population

A retrospective study was applied for this research where the hospital records of patients were reviewed and analyzed in order to answer the objectives of this research among end stage renal disease (ESRD) patient undergoing CAPD treatment from January 2011 to December 2016. The study was conducted at CAPD Unit, Nephrology Department, HTAA. Inclusion criteria: ESRD patients older than 18 years of age who were on continuous ambulatory peritoneal dialysis (CAPD). Exclusion criteria: non ESRD patients, patients with ESRD but not treated by CAPD, passed away patients, and those initially treated with CAPD but then converted to other dialysis modalities.

Sample size calculation was done by referring to the total number of continuous ambulatory peritoneal dialysis (CAPD) patients in HTAA from January 2011 till December 2016 as reference population. The unpublished data from CAPD audit showed that total number of CAPD patients in Nephrology Clinic, HTAA between the timeline was 182 patients. In order to achieve 95% of confidence level with 5% of confidence interval, the minimum sample size needed for this study is 137. After considering all the criteria as above, 74 patients were included in this study.

Data collection

The following data were collected for all patients: socio-demographic details (identification number, age, sex, race, body mass index (BMI), duration of CAPD treatment, primary disease and comorbidities) and biochemical analysis data (serum phosphate, serum calcium, intact parathyroid hormone (iPTH), serum albumin, normalized protein catabolic rate (nPCR), peritoneal equilibration test (PET) characteristic, calcium carbonate ($CaCO_3$), total creatinine clearance, residual renal creatinine clearance, 24-hours urine volume output). Socio-demographics data were recorded at baseline while for biochemical analysis data were collected from the latest results.

Statistical test

Descriptive test was used for all demographic data listed. Continuous data were expressed as a proportion and medians or means ± standards deviation, according to the nature of the data for

this study while categorical variables were expressed as percentages. Simple linear regression was used to identify the possibly independent predictors of hyperphosphatemia among continuous ambulatory peritoneal dialysis (CAPD) patients. The search of association between phosphate level and the PET characteristic in CAPD patients were test using Pearson's correlation coefficients. Statistical evaluation was carried out with the Statistical Package for the Social Sciences (SPSS) version 22.0 and Graph Pad Prism 6, at a level of *p*-value less than 0.05 ($p < 0.05$) is considered statistically significant.

RESULTS

Between January 1, 2011, and December 31, 2016, a total of 74 adult patients on CAPD modalities were enrolled for this study. The average duration of peritoneal dialysis is 21.9 ± 16.1 months (range 3-73 months). Age was defined with age at the time of data collection and was classified into 6 groups; 15-24, 25-34, 35-44, 45-54, 55-64, ≥ 65. The patient's mean age is 51.34 ± 13.75 year (range 24-82) with dominantly 28.38% in the age group 55-64 years and only 2.7% in the age group of 15-24 years. The overall trends for patient's age distribution to be increasing but then decline for patient's age more than 65 years. There was no further documentation on the type of diseases or conditions that contributed to the unknown causes of the patients' medical records as the exact diagnosis is not known. All patients received calcium carbonate (CaCO3) treatment appropriately in accordance to the phosphate level following strictly the Kidney Disease: Improving Global Outcomes (KDIGO) (2003) guidelines and were not influencing this study. The population characteristics and distribution can be observed in Table 1.

Table 1 Characteristics of the Peritoneal Dialysis Patients (n = 74)

	n/%
Gender n (%)	
Male	41 (55.4%)
Female	33 (44.6%)
Age (years)	
Mean ± SD	51.34 ± 13.75
Range	24-82
15-24 years old	2 (2.7%)
25-34 years old	10 (13.52%)
35-44 years old	11 (14.86%)
45-54 years old	18 (24.32%)
55-64 years old	21 (28.38%)
≥65 years old	12 (16.22%)
Ethnicity n (%)	
Malay	65 (87.8%)
Chinese	6 (8.1%)

Indian	3 (4.1%)
BMI (kg/m^2) n (%)	
Underweight	6 (8.1%)
Normal	38 (51.4%)
Overweight	21 (28.4%)
Obese	9 (12.2%)
Primary Disease n (%)	
Diabetes	26 (35.1%)
Glomerulonephritis	1 (1.4%)
Hepatitis B	1 (1.4%)
Sytemic Lupus Erythematosus (SLE)	3 (4.1%)
Unknown Disease	42 (56.8%)
Comorbidities n (%)	
Hypertension (HTN)	38 (51.4%)
Hyperparathyroidism (HPT)	18 (24.3%)
Hypertension/Hyperparathyroidism	11 (14.9%)
Anemia/ Hyperparathyroidism	7 (9.5%)

Peritoneal Equilibration Test (PET) characteristics

The distribution of PET characteristics of all CAPD patients (n= 66) in our population was predominant low average transport status followed by high average, high and low transport status with 35.1% (n= 26), 32.4% (n= 24), 14.9% (n= 11) and 6.8% (n= 5) correspondently. In addition, patients with high phosphate level (n= 37, 50%) also characterized according to peritoneal transport status and shows that 40.5% (n= 15) classified under low average, followed by high average, high and low transport status with 29.7% (n= 11), 10.8% (n= 4) and 8.1% (n= 3) respectively.

Serum phosphate level

The present study discovered that there were 37 CAPD patients (50%) presented with high phosphate level after starting the treatment while the rest shows normal phosphate level. From a total of 55.4% (n= 41) male patients on CAPD modalities, 57% (n= 21) presented with high phosphate level. While, 43% (n= 16) female patients presented high phosphate level from a total of 44.6% (n= 33).

Risk factors of hyperphosphatemia

Linear regression was performed to predict and analyze the association between the serum phosphate levels with other factors. The most striking result to emerge from the data is that normalized protein catabolic rate (nPCR), serum calcium, serum albumin, intact parathyroid hormone (iPTH) and 24-hours urine volume output taken together, these results suggest that there were significant association between the factors with the serum phosphate level. Factor

like age, total creatinine clearance, residual renal creatinine clearance were found to be inversely associated with this level. In contrast, body mass index (BMI) and peritoneal dialysis duration, were not significantly associated with the amount of serum phosphate (Table 2).

Table 2 Factors associated with serum phosphate level

FACTOR	MEAN± SD	r	*p*-value
Age (years)	51.34 ± 13.75	-0.321	0.0052*
BMI (kg/m^2)	24.5 ± 5.3	-0.102	0.3876
Dialysis Duration (month)	21.9 ± 16.1	0.097	0.4131
nPCR (g/kg*d)	0.72 ± 0.18	0.299	0.0126*
Serum Calcium	2.22 ± 0.29	0.302	0.0090*
Serum Albumin (g/dl)	34.96 ± 5.51	0.261	0.0244*
iPTH (per 100ng/dl)	186.88 ± 148.43	0.373	0.0012*
Total Creatinine Clearance	60.22 ± 19.87	-0.220	0.0470*
Residual Renal Creatinine Clearance	15.20 ± 20.62	-0.422	0.0390*
24-hours urine volume output	294.37 ± 330.97	0.441	0.0060*

*significant with *p*-value < 0.05

Association of phosphate level and PET characteristics

A scatter diagram and a Pearson's product moment correlation were used to assess the relationship between phosphate level and peritoneal membrane characteristics. Prior to direct comparison between phosphate level and peritoneal membrane status, however, have not shown a clear significant difference in this analysis. Data analysis showed there was a weak, negative correlation between phosphate level and PET characteristics (r = -.232, n= 66, p = 0.070). This study then attempted to examine based on peritoneal membrane transport alone and finding shows that it is significantly correlated with peritoneal clearance (r= 0.4748, n= 66, p < 0.001). High and high average membrane status have higher peritoneal clearance while low and low average membrane status have a lower peritoneal clearance (Table 3).

Table 3 Transport categories and peritoneal clearance

Membrane transport type	MEAN± SD Peritoneal clearance (L/week/1.73 m^2)
High Transport	71.87 ± 22.07

High Average Transport	59.45 ± 16.63
Low Average Transport	55.10 ± 20.68
Low Transport	33.58 ± 6.03

DISCUSSIONS

In this retrospective study, it is demonstrated that 74 adult patients were admitted for continuous ambulatory peritoneal dialysis (CAPD) treatment in Hospital Tengku Ampuan Afzan (HTAA). Gender differences have been identified where end stage renal disease (ESRD) cases for male are notably higher than females. It is important to evaluating clinical data by gender because of men's and women's physiology differences. These results are consistent with those of other studies and suggested that predictors leading to decline in renal function are related with gender differences (Halbesma et al., 2008; Hecking et al., 2014).

Comparing the distribution of ethnicity of CAPD patients treated in HTAA showed that Malay race covers the majority of the study population compare to Chinese and Indian. A possible explanation for this might be that the patients was from the states of Pahang in Malaysia, where probably the dominant ethnic group is Malay. Study by Sabanayagam and colleagues in 2013 stated, the differences of ethnicity distribution in CKD might be influenced by the association with prevalence disease such as hypertension and medication received by the patients. Higher cases of CKD in the elderly population has been connected to the fact that renal function declines with age. One unanticipated finding in this study is that predominance body mass index (BMI) categories of CAPD patients was normal followed by overweight, obese and underweight. Surprisingly, other findings indicate so called the obesity paradox where being overweight/obese or high value of BMI are actually a protection and associated with improve survival on hemodialysis (Ikizler, Stenvinkel, & Lindholm, 2008) but mixed result is seen for peritoneal dialysis patients (Park et al., 2014). The association of BMI and peritoneal dialysis survival has been inconsistent as of result on previous study shows neutral (Aslam, Bernardini, Fried, & Piraino, 2002) beneficial (Johnson et al., 2000) and damaging (McDonald, Collins, & Johnson, 2003) effect of high BMI toward peritoneal dialysis outcome.

The status in peritoneal membrane transport is related to the long term survival dialysis patients. High transport status demonstrated to be associated with the mortality rate and an independent predictor for technique failure for patients that subscribed to CAPD modalities (Rumpsfeld, Mcdonald, & Johnson, 2006). However, the findings by Huang and colleagues (2014) do not support previously findings where high transport status does not necessarily add to adverse effect in survival rate when diabetes status included, suggesting that, factor such as causes of end stage renal disease (ESRD) may influenced patients transport status. To add to that, other findings by Park and colleagues (2001), Paniagua and colleagues (2002), and Perl and colleagues (2009) also reported that high peritoneal transport status failed to independently influence mortality rate in CAPD patients. This inconsistency not clearly represented but may

be due to differences in the primary diseases and comorbidities of ESRD, racial or ethnicity of patients, method of the PET test and a combination of new and prevalent cases. These findings may help to understand and be used to guide dialysis modalities that are appropriate for each patients when the evaluation of peritoneal membrane be performed routinely. In further management, the use of this data could be a means optimizing medical prescription according to the result of the peritoneal membrane status.

An initial objective of the research was to determine the prevalence of CAPD presented with hyperphosphatemia in Nephrology Clinic, HTAA after starting the treatment. In this population it is found that half of the patients (50%, n= 37) with 21 male (56.8%) and 16 female (43.2%) were presented with a high phosphate level. This result may suggest that hyperphosphatemia should be taken into concern and prior studies have highlighted the importance of maintaining phosphate level in end stage renal disease (ESRD) patients. This finding has important implications for the management of hyperphosphatemia in dialysis patients that include dietary management and the use of medication and phosphate binders according to the stages of CKD development. Further studies, which take these variables into account, will need to be undertaken.

As mention previously, understanding the importance of serum phosphate level is crucial for end stage renal disease (ESRD) patient as it is contribute to the risk of diseases where the controlling may be useful to improve ESRD prognosis. Therefore, an additional findings on hyperphosphatemia risk factors was performed to achieve better phosphate control.

In this study we found that normalized protein catabolic rate (nPCR), serum calcium, serum albumin, intact parathyroid hormone (iPTH), 24-hours urine volume output, age, total creatinine clearance, residual renal creatinine clearance were independent risk factors for hyerphosphatemia. Increased or decreased amount of serum phosphate level is influenced by various variables that comprise of phosphate intake, phosphate absorption and phosphate removal. It can therefore from these results be assumed that, dietary phosphate intake, dialysis adequacy and calcium phosphate metabolism determines the serum phosphate level. Hence, it is useful to be noted that directly treating phosphate through restriction and control of dietary phosphate intake may be useful in slowing and controlling the progression vascular calcification, cardiovascular and bone disease (CKD-MBD) as well as secondary hyperparathyroidism (SHPT) in later kidney disease stages. In order to provide a better clinical outcomes, earlier approach of phosphate binder therapy, prescription of supplement (vitamin D) concomitant to dietary intake was suggested (Martin & González, 2011).

This study set forth with the aim of assessing the relationship of the PET characteristics toward phosphate level among CAPD patients in Nephrology Clinic, HTAA. This study did not conclude a significant correlation between serum phosphate level and peritoneal membrane transport status when direct correlation was performed. In this study, peritoneal membrane characteristic was determined according to the calculation of peritoneal membrane creatinine transport status. According to the principle of diffusion across the peritoneal membrane,

phosphorus is considered as large size molecules based on its molecular weight, hence, rate of phosphate clearance across the peritoneal membrane is more likely to be similar to creatinine (Nissenson & Fine, 2017).

Previous research however, mentioned that peritoneal creatinine transporter (D/P Cr) and clearance (CrCl) cannot be used as substitutes to indicate peritoneal phosphate transport status (D/P Ph) and phosphate clearance (PhCl) from which in the result reported that D/P Cr and CrCl does not show any significant differences between normal and hyperphosphatemia patients while those with hyperphosphatemia showed significant association with D/P Ph (p = 0.019) and PhCl (p = 0.06) (Courivaud & Davenport, 2015). Contradictory to this, multivariate regression analysis in a retrospective study stated that creatinine clearance can be a substitutes to phosphate clearance as there is strong independent association between both (Badve, Zimmerman, Knoll, Burns, & McCormick, 2008). Another study by López-guerra, Rodríguez-garcía, and Rodríguez-castellanos in 2014 also mentioned that phosphate clearance showed to be significantly correlated with creatinine clearance in total, dialysate and urine measurement with $p < 0.05$. The inconsistency of current finding with preceding study suggest the possibility on the different in the 4-hours (D/P ratio) solute range of PET classification and the methods of the PET test.

The main limitation of our study were a short study period and relatively small patient population size. To counteract those limitations, a prospective or retrospective cohort study can be done. Continuity of research in regard of these indicators are recommended on the basis of lacking on the knowledge about phosphorus transport especially for patients undergo peritoneal dialysis modalities in clinical practices suggesting that it may possible to compare the variables between CAPD modalities with other type of treatment such as APD. Large sample size that possibly include other government and/or private hospitals and/or clinics could be included for this study. Multicenter study that covers other hospitals such as from other district in Pahang or possibly expand it to Malaysia that covers major hospital in the Peninsular so that can include all main corridors; northern, westerns, eastern and southern.

CONCLUSION

In conclusion, the prevalence of hyperphosphatemia among continuous ambulatory peritoneal dialysis (CAPD) patients is considered as high and have become one of the major concern by nephrologist and health professionals due to the clinical consequences. Based on this research, level of serum phosphate was significantly, positively associated with nutritional markers (normalized protein catabolic rate (nPCR) and serum albumin), intact parathyroid hormone (iPTH), serum calcium and 24- hours urine volume output. Serum phosphate level was significantly, inversely associated with age and dialysis adequacy (total creatinine clearance and residual renal creatinine clearance). While, body mass index (BMI) and duration on dialysis were found to be not significantly associated with serum phosphate level among CAPD patients in HTAA. In this investigation, the main goal was to assess the correlation between serum phosphate level and peritoneal equilibration test characteristics or the transport status.

Returning to the question posed at the beginning of this study, it is now possible to state that there was no significant correlation between serum phosphate level and PET characteristics given the rate of the toxin removal (phosphate) should not been affected by the differences on peritoneal membrane status. The study has gone some way towards enhancing our knowledge on the important of adequacy and efficiency of solute clearance in dialysis patient to reduce rate of morbidity and mortality and subsequently improve patient's management.

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