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The relationship between bone mineral indices and survival in patients on peritoneal dialysis

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ABSTRACT

Introduction: Disorders of minerals metabolism are common metabolic problems in patients undergoing peritoneal dialysis (PD) which causes increase in mortality and morbidity in these patients.
Objectives: In this study, the relationship between bone metabolic indices and mortality rate in patients on PD was assessed.
Patients and Methods: Data were collected from Iranian peritoneal dialysis registry database, covering the period 2009–2015 and comprised 2000 adult patients. Patients with less than three months follow-up and incomplete data were excluded. Demographic and some laboratory data (including age, gender, body mass index, serum albumin, dialysis vintage and comorbidities) of patients recorded. Additionally, the unadjusted and adjusted, hazard ratios (HRs) of serum phosphorus (P), calcium (Ca) and parathyroid hormone (PTH) levels, to find their association with mortality were calculated, using the Cox proportional-hazards model.
Results: In total, 1197 out of 2000 patients had the inclusion criteria and were included in the study. We found that serum iPTH (intact parathyroid hormone) over 600 pg/mL significantly increased the mortality rate by 2.7 times compared to iPTH levels between 200 to 600 pg/mL (HR: 2.7, $P=0.002$). Additionally, the serum phosphorus level less than 4 mg/dL was significantly ($P=0.0001$) related to higher mortality rate (HR: 1.6). There was no significant association of serum calcium and alkaline phosphatase (ALP) levels with mortality ($P>0.05$).
Conclusion: Although high serum iPTH and low-serum phosphorus levels could determine the mortality risk in PD patients, Ca and ALP levels were not risk factors for mortality.

Implication for health policy/practice/research/medical education:
Chronic kidney disease-mineral bone disorder is a major problem in the end-stage renal disease patients. The impact of altered bone- mineral elements in hemodialysis patients has been evaluated in literature; however, its effects on patients who use peritoneal dialysis (PD) for renal replacement therapy is under debate. In this study, we used data from a large sample size of PD patients to evaluate the relation between bone metabolic indices and mortality rate in these patients. We found that the serum phosphorus level less than 4 mg/dL significantly related to higher mortality rate while neither serum calcium nor alkaline-phosphatase showed association with higher mortality.
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Introduction

Patients with moderate and advanced chronic kidney diseases (CKD) are commonly suffering from abnormalities in serum levels of calcium (Ca), phosphorus (P), and parathyroid hormone (PTH). Chronic kidney disease–mineral and bone disorder (CKD–MBD) as a systemic syndrome is a spectrum of disorders manifested by the abnormal laboratory levels of Ca, P, PTH and disturbed vitamin D metabolism and bone turnover (1). In patients on routine dialysis, such abnormalities are related to both all-cause and cardiovascular mortality elevation (2,3). Notably in end-stage renal disease (ESRD) patients, the principal cause of mortality is cardiovascular disease (CVD) since; studies have shown that cardiovascular attributed mortality risk in ESRD subjects is 10- to 20-fold higher than general population (2). Although the causes of the CKD-MBD and its effects on cardiovascular is still under investigation, studies showed that some

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non-traditional cardiovascular risk factors including hyperphosphatemia, vascular calcification, and elevated fibroblast growth factor 23 (FGF23) levels occur within the CKD-MBD (4). The CKD-MBD begins with the early stages of CKD with vascular dedifferentiation/ calcification, an ecommends maintaining the ser osteodystrophy and increased FGF23 secretion (4).

Results from several studies have indicated that adverse cardiovascular events and mortality in dialysis patients are associated with high levels of P and Ca (2,6-7), higher (6,7) or lower (8) than target levels of PTH, and elevated alkaline phosphatase (ALP) levels (9). Based on these epidemiological and clinical evidence, Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for CKD-MBD recommend maintaining the serum levels of these important factors in required range (10).

It is noteworthy that while PD remains the healthiest way to start renal replacement therapy in ESRD patients, however the majority of CKD-MBD studies has focused on hemodialysis patients and there is a relatively small number of studies evaluating this matter in PD patients (11-13). The basis for current management of CKD-MBD in PD patients mostly comes from limited studies that showed an association between ALP level and mortality in patients on maintenance PD (11,13).

Objectives

In this study, we aimed to retrospectively evaluate the association of CKD-MBD biomarkers, namely, serum Ca, P, PTH and ALP, with patient's survival in a population of patients on maintenance PD.

Patients and Methods

Study design

In our country, we have a computerized PD data system that collects data from 36 PD centers treating patients throughout the country called "Iranian Peritoneal Dialysis Registry- IPDR". In brief, this registry collects data on socio-demographics, clinical and laboratory characteristics of PD patients as well as treatments and follow-up. In this retrospective observational study, we used the data of all adult patients who enrolled in this registry from 2009 to 2015. Inclusion criteria were age older than 15 years, and being on PD for longer than three months. Patients who had incomplete data, and those who had renal transplantation or switch to hemodialysis were excluded from the study.

Demographic and PD-related variables including age, gender, and body mass index and also underlying causes of ESRD were obtained from the Iranian PD registry database. The first three available constitutive measurements of laboratory data including hemoglobin (Hb), albumin, Ca, P, iPTH (intact parathyroid hormone) and ALP were recorded and the mean of these three measurements was included for data analysis.

Data analysis

Data were analyzed by SPSS version 20.0 software. The means and standard deviations used for presentation of numerical variables and the frequency and percent were reported for categorical variables. The Kaplan-Mayer survival analysis was conducted for survival. The Cox regression analysis was used to determine contributing factors and hazard ratio associated with survival while controlling for confounding factors. The survival time for each patient was the time being on PD until death. The *P* values of less than 0.05 considered statistically significant.

Results

In this study, among 2000 existing medical documents, 1197 cases had completed optimal data and were therefore enrolled in the study. Among them 607 patients were female (50.7%) and 590 subjects (49.3%) were male. The mean age of subjects was 66.9 ± 10.6 years (Table 1). During the study period, 209 patients died from which the most common cause of death was cardiovascular events (63.2%).

Looking at the survival of patients showed that the mean total survival was 75.4 months for all patients (Figure 1) while the one-year and three-year survival rates were 93.2% and 73.6% in our patients, respectively. There was a significant difference in one and three years survival of patients when PD patients were divided based on iPTH level (Table 2). We found that patients with iPTH levels higher than 600 pg/mL had the lowest rate of one and three years survival (57.1% and 28.6%, respectively) while patients who had the iPTH levels lower than 150 pg/mL had the highest rate of one and three years survival ($P = 0.0001$).

In non-adjusted regression analysis, the variables of age, serum albumin, estimated GFR based on creatinine clearance measured in a 24-hour urine collection, iPTH and P had a significant effect on mortality risk. In multivariate regression analysis, we adjusted for confounding factors of albumin, GFR and age and found that mortality risk in patients with iPTH over 600 pg/mL, was 2.7 (95% CI: 1.4-5.2) times higher when compared to iPTH level 200-600 pg/mL (Table 3). Noteworthy, the mortality risk in patients with P level less than 4 mg/dL was 1.6 (95% CI: 1.1-2.2) times higher compared to patients with P between 4 and 6 mg/dL ($P < 0.001$).

When we categorized the anthropometric and laboratory data of our patients based on their serum iPTH level, we found that majority of patients had a serum iPTH level of 150-300 pg/mL (54.2%). Notably, the reference range for iPTH levels in our laboratory is 10-65 pg/mL. We found that the serum Ca ($P = 0.02$) and albumin levels ($P = 0.03$) were the only factors that had an association with iPTH level (Table 4).

Discussion

Previous reports have identified associations among

Table 1. The anthropometric and laboratory characteristics of enrolled patients

Variable	Mean (SD), N= 1197	Range
Age (year)	66.9 (10.6)	31-95
Sex (male/female), n (%)	590/607 (50.7/49.3)	
BMI (kg/m^2)	23.7 (4.38)	13.3-60.09
Comorbidities, n (%)		
HTN	444 (37)	
DM	356 (29.7)	
Cardiovascular	54 (4.5)	
Cerebrovascular	28 (2.3)	
Cirrhosis	8(0.6)	
Cancer	2 (0.16)	
Respiratory	3 (0.25)	
Others	12 (1)	
Cause of ESRD, n (%)		
DM	308 (25.7)	
HTN	294 (24.6)	
Collagen vascular disease	25 (2.1)	
Glomerulonephritis	74 (6.2)	
PKD	50 (4.2)	
Others	175 (14.5)	
Unknown	271 (22.6)	
GFR (mL/min)	4.2 (4.67)	
Kt /V	1.81 (0.34)	0.44-2.92
Hemodialysis vintage(months)	1.91 (0.49)	
Serum albumin (g/dL)	3.83 (0.56)	1.5-5.7
Hemoglobin (g/dL)	11.48 (1.42)	8.40-17.70
Serum albumin (g/dL)	3.83 (0.56)	1.5-5.7
Calcium (mg/dL)	8.95 (0.59)	7.0-11.9
Phosphorous (mg/dL)	4.67 (1.17)	2.10-7.80
Alkaline-phosphatase (U/L)	331 (105.0)	149.0-845.0
iPTH (pg/mL)	166.85 (75.40)	55.0-690

BMI: Body mass index, HTN: Hypertension, DM: Diabetes Mellitus, ESRD: End stage renal disease, PKD: Polycystic kidney disease, GFR: glomerular filtration rate, iPTH: intact parathyroid hormone.

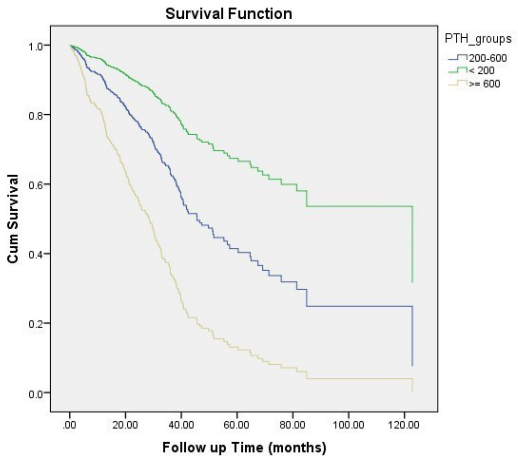

Figure 1. Survival of included peritoneal dialysis patients based on enrollment iPTH levels.

Table 2. Mean, 1 and 3- year survival of study patients based on categorized PTH level

Serum iPTH	Survival			*P* value
	Mean SD	1 year	3 year	
Total	75.43 (69.03-81.82)	93.2%	73.6%	0.0001
<150 pg/mL	101.66 (93.58-109.74)	96.4%	86.3%	
150-300 pg/mL	58.34 (52.72-63.95)	91.7%	66.1%	
300-600 pg/mL	32.23 (22.80-41.67)	76.2%	65.3%	
≥ 600 pg/mL	23.51 (11.82-35.20)	57.1%	28.6%	

PTH: intact parathyroid hormone
P < 0.05 defined as significant level.

Table 3. Cox multivariate regression analysis of survival

Variable	Survival			
	Non-Adjusted		Adjusted	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male	0.9 (0. 7-1.3)	0.6		
Age (y)	1.0 (1.01-1.0)	0.00	1.0 (1.01-1.0)	0.00
BMI (kg/m^2)	1.0 (0.99-1.1)	0.1	1.01 (0.99-1.1)	0.07
Serum albumin (g/dL)	0.7 (0.5-0.9)	0.00	0.7 (0.5-0.9)	0.00
Hemoglobin (g/dL)	0.9 (0.8-1.0)	0.1	0.9 (0.8-1.01)	0.06
GFR (mL/min)	1.0 (1.0-1.1)	0.01	1.0 (1.02-1.1)	0.00
Hemodialysis-vintage (m)	1.02 (0.7-1.4)	0.9		
Kt/V	1.1 (0.7-1.7)	0.7		
iPTH (pg/mL)				
<200	0.4 (0.3-0.6)	0.00	0.4 (0.3-0.6)	0.00
≥600	2.8 (1.4-5.5)	0.00	2.7 (1.4-5.2)	0.00
Phosphorous (mg/dL)				
<4	1.6 (1.1-2.3)	0.01	1.6 (1.1-2.2)	0.01
≥6	1.5 (0.9-2.4)	0.09	1.4 (0.9-2.2)	0.1
Calcium (mg/dL)				
≥10	1.1 (0.6-2.1)	0.7		
ALP (U/L)				
200-299	1.6 (0.8-3.4)	0.2		
300-399	1.3 (0.6-2.6)	0.5		
≥400	1.4 (0.6-2.9)	0.4		
Comorbidity				
HTN	0.8 (0.3-2.2)	0.6		
DM	1 (0.3-2.8)	0.9		
Cardiac disease	0.7 (0.2-2.1)	0.5		
Vascular disease	1.8 (0.5-6.1)	0.4		

HR: hazard ratio, BMI: Body mass index, GFR: glomerular filtration rate, PTH: intact parathyroid hormone, HTN: hypertension, DM: diabetes mellitus; ALP, alkaline phosphatase.
P < 0.05 defined as significant level.

disorders of mineral metabolism and all-cause mortality in ESRD subjects, employing data mostly from hemodialysis patients. However, in this study we pooled data from our Iranian PD registry during 6 year period and showed that among mineral abnormalities, the iPTH serum levels

Table 4. The association of anthropometric and biochemical data of patients with categorical level of serum iPTH

Variable	PTH level (pg/mL)				*P* value
	<150	150-300	300-600	>600	
N total, (%)	520 (43.4)	649 (54.2)	14 (1.2)	14 (1.2)	
Sex					
Male, n (%)	254 (48.8)	319 (49.2)	7 (50)	10 (71.4)	0.4
Female, n (%)	266 (51.2)	330 (50.8)	7 (50)	4 (28.6)	
Age (year), n (%)	67.5 (10.92)	66.34 (10.4)	66.36 (9.8)	68.9 (11.7)	0.2
BMI (kg/m²), n (%)	23.7 (4.2)	23.7 (4.53)	23.67 (4.57)	23.9 (2.95)	0.9
Serum alb (g/dL), n (%)	3.83 (0.56)	3.8 (0.54)	3.99 (0.3)	3.39 (0.8)	0.03*
Hg (g/dL), n (%)	11. (1.43)	11.46 (1.4)	11.2 (1.04)	11.49 (1.6)	0.9
GFR, n (%)	4.1 (4.26)	4.38 (4.31)	3.64 (3.65)	2.53 (2.27)	0.3
Hemodialysis vintage (months), n (%)	1.92 (0.47)	1.9 (0.5)	1.96 (0.3)	2.19 (0.5)	0.2
Kt/V, n (%)	1.8 (0.35)	1.8 (0.3)	1.6 (0.5)	1.7 (0.27)	0.2
Phosphorous (mg/dL), n (%)	4.56 (1.08)	4.76 (1.25)	4.64 (1.09)	4.5 (1.1)	0.2
Calcium (mg/dL), n (%)	9.01 (0.6)	8.9 (0.58)	9.01 (0.7)	8.94 (0.5)	0.02**
ALP (U/L), n (%)	331.6 (109)	332.8 (100.6)	314.9 (146.4)	327.4 (118.2)	0.4

BMI: Body mass index, GFR: glomerular filtration rate, iPTH: intact parathyroid hormone, ALP, alkaline phosphatase.
* iPTH >600 versus all other PTH category. **iPTH <150 versus iPTH 150-300.

of higher than 600 pg/mL and P levels less than 4 mg/dL are associated with 2.7 and 1.6 times higher mortality risk among PD patients, respectively. In addition to enrollment serum levels of P and iPTH, in this study, we found other demographic and bio-chemical risk factors of increased mortality including age and serum albumin. To our knowledge, this is the first study that evaluates the relation between bone mineral parameters and survival in an Iranian PD population.

Secondary hyperparathyroidism is a usual consequence of progressive renal failure. In addition to the potentially devastating bone disease, many uremic manifestations including neurotoxicity, cardiomyopathy, impaired insulin secretion, abnormal lipid and protein metabolism, impaired immune function, and metabolic acidosis have been attributed to high iPTH levels in PD patients (14).

In addition to above adverse effects, some studies have shown that abnormal levels of iPTH have been related to risk of mortality. Accordingly, here we showed that serum iPTH higher than 600 pg/mL is associated with mortality risk in PD patients. Consistent with these results, Block and colleagues evaluated the data on more than 40 000 hemodialysis patients and showed that moderate to severe hyperparathyroidism (iPTH concentrations ≥600 pg/mL) was associated with an increase in the relative risk of death (7). Data from the dialysis outcomes and practice patterns study showed that mortality was higher among patients with high iPTH levels >600 pg/mL (2).

Interestingly, Avram et al prospectively evaluated the data of 277 PD patients for 14 years. They found that patients with enrollment iPTH greater than 200 pg/mL had significantly better survival than patients with iPTH 65 to 199 pg/mL (15). These effects were seen with and without adjustment for factors of age, race, gender, months on dialysis at enrollment, diabetic status and nutritional markers that traditionally known to influence mortality.

Accordingly, Avram and colleagues in a retrospective study showed that four-year PD survivors had significantly higher iPTH levels at enrollment of dialytic therapy than did those with shorter survival (14). They speculated that patients with higher iPTH (higher than 200 pg/mL) were better nourished than patients with lower iPTH and that might contribute to better survival of these patients. Although by this study we cannot discuss the mechanisms underlying the increase in mortality associated with disturbed mineral metabolism, some studies showed that iPTH can stimulate the transformation of vascular smooth muscles into osteoblast. These osteoblasts are able to produce pro-mineralizing milieu which in turn could accelerate the super-saturation of extracellular Ca and P and development of medial wall vascular calcification. These processes are recognized to be associated with increased arterial stiffness, aortic pulse wave velocity, left ventricular size with subsequent all-cause mortality (15-17). Other involved mechanisms may include the augmentation of risk of arrhythmic events due to accumulation of Ca in myocardium and impairment of cardiac energy production (18).

In our study, we found that phosphorous level less than 4 mg/dL was related to mortality.

In an international study Tentori and colleagues collected data during 10 years period in concept of dialysis outcomes and practice patterns study from 12 countries and found that the greatest risk of mortality was found for Ca levels greater than 10.0 mg/dL, phosphorus levels greater than 7.0 mg/dL, and iPTH levels greater

than 600 pg/mL (2). It should be noted that in our study, we evaluated the enrollment levels of iPTH and P for assessing the mortality risk in PD patients while in the study by Tentori et al, the baseline and at 4 months interval laboratory measurement were considered for analysis.

In the study by Kang and colleagues, the association between CKD-MBD biomarkers and all-cause mortality was found to be inconsistent when baseline measurements or time-varying covariates were employed in statistical models of predicting mortality. They suggested that in a cohort study with a long follow-up period, using the baseline predictors variables of survival might be preferred since these measurements could ease the important fluctuations in these factors across the study period (19). This point should be considered when data across different studies are compared and might be one of the reasons behind different results obtained by studies.

We have also to note that we could not find an association between Ca levels and mortality, while some studies have shown that abnormal levels of Ca can increase the risk of mortality.

For example in a cohort study comprised of 25 588 patients on chronic hemodialysis, both all-cause and cardiovascular mortality were greater at calcium levels higher than 10.0 mg/dL (2). Rivara et al (20) demonstrated that Ca level less than 8.5 and more than 10.2 mg/dL and the phosphorous level more than 6.4 mg/dL were related to higher mortality rate in PD cases. Tentori et al (2) reported the least mortality rate in those with calcium, phosphorous, and iPTH of normal range, while the mortality increased when calcium and phosphorous, levels reached levels higher than 10 mg/dL and 7 mg/dL, respectively. Although we cannot completely explain the observed difference between results, however the different study type and design and also the high number of patients in our study might be the underlying causes for seeing such difference.

Conclusion

In conclusion, in this retrospective study with relative high number of PD patients, we found that iPTH level higher than 600 pg/mL is associated with higher mortality risk. Our results could not recognize the PD enrollment levels of Ca and ALP as the risk factor for mortality in these patients. Use of other study designs such as randomized clinical trials to determine the optimal ranges for bone metabolic indices and mortality pattern in patients after essential interventions may develop more definite results in patients on PD, especially if optimal statistical assays are used with adjustment for confounding factors.

Limitations of the study

The data for some patients were missing and some data regarding creatinine clearance and transport status of peritoneum were not available.

Authors' contribution

FY and HT were the principal investigators of the study. FY, HT and SA prepared the manuscript. MH revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declared no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Tehran University of Medical Sciences approved this study. The institutional ethical committee at Tehran University of Medical Sciences approved all study protocols (IR-TUMS.MEDICINE.REC.1396.2513). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from the M.D thesis of Hannaneh Taghizadeh at this university (Thesis #9211160008). Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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