The Importance Calcium Phosphorus Product in Renal Insufficiency

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ABSTRACT

High serum phosphorus (P) levels in chronic renal failure (CRF) lead to parathyroid hormone (PTH) resistance of skeletal system. Serum calcitriol level increases and calcium (Ca) reabsorbtion from intestine decreases. Because of these abnormalities calcifications occur in soft tissues and perivascular tissues. Cardiovascular complications occur and high CaxP product levels seen in laboratory results. Our aim was to find out the critical level of CaxP product in different treatment groups of patients with CRF. CRF patients who did not require dialysis before (preD, N=36), chronic renal disease patients on peritoneal dialysis (PD, N=36), chronic renal disease patients receiving hemodialysis treatment (HD, N=35), renal transplant patients (Tx, N=36), and healthy individuals (N=30) evaluated for the study. Total of 173 patients (77 male, 96 female) included to the study. Patients body mass indexes calculated. Blood levels of PTH, Ca, P and cystatin C (CysC) levels were measured (Siemens Healthcare Diagnostics, USA). Kolmogorov-Smirnov test is used to check the normality of data among groups. One Way Analysis of Variance is used for normally distributed groups. For non-normally distributed data, Kruskal Wallis Analysis of Variance is used for comparison of groups. Associations between categorical variables are assessed using the cross-tables and Chi-squared tests. The Receiver operating characteristics (ROC) analysis is used to measure the performance of biochemical parameters in detecting kidney dysfunction. Greater than 1mg/dL CysC levels accepted as renal dysfunction. The cut-off value for CaxP product was obtained as 37.535. Area under the ROC curve was 0.678 (p=0.002), the sensitivity and specificity were 0.573 and 0.800, respectively. Median value of all groups for CaxP was found as 37.730; very near the cut-off value (37.535). There was a significant difference in CysC levels between the two groups of dialysis according to cut-off value of 37.535. (p<0.05) In our study according to ROC analysis results, CaxP product critical value for all the patients which grouped according to treatment modalities is 37,535. In serum Ca and P parameters show high measurement performance and CaxP value is easy to access. The critical value that we found in our study groups should be confirmed for detection of renal failure and cardiovascular complications in future research.

Key Words: *Chronic renal disease, calcium, fosfor, cycstatin C*

Böbrek fonksiyon bozukluğunda kalsiyum × fosfor çarpımının önemi

ÖZET

Kronik böbrek yetmezliği (KBY)'nde yüksek serum fosfor (P) düzeyleri iskelet sisteminde parathormon (PTH) direncine neden olur. Serum kalsitriol düzeyi ve barsaktan kalsiyum (Ca) emilimi azalır. Tüm bu bozuklukların sonucunda yumuşak doku ve vasküler yapıda kalsifikasyon gelişir. Kardiyovasküler komplikasyonlara laboratuvarda yüksek (Ca×P) düzeyleri eşlik eder. Bizde çalışmamızda değişik tedavi gruplarından oluşturulan KBY hastalarında Ca×P seviyelerinin kritik değerini belirlemeyi amaçladık. KBY tanısı almış olup, henüz diyalize alınmamış (preD, N=36), periton diyalizi uygulanan (PD, N=36), hemodiyaliz uygulanan (HD, N=35), transplantasyon yapılmış (Tx, N=36) olan hastalar ve sağlıklı bireyler (N=30) olmak üzere 173 olgu (77 erkek, 96 kadın) çalışmaya alındı. Vücut kitle indeksleri hesaplandı, serum PTH, Ca, P, Sistatin C düzeyleri belirlendi (Siemens Healthcare Diagnostics, USA). Grupların normal normal dağılıp dağılmadığı Kolmogrov-Smirnov testi ile kontrol edildi. Normal dağılan gruplar için Tek Yönlü Varyans Analizi ile, normal dağılmayan gruplara ise Kruskal Wallis Varyans Analizi testi ile gruplar arası karşılaştırma yapıldı. Kategorik değişkenler arası ilişki için çapraz tablolar ve ki-kare testleri kullanıldı. Böbrek fonksiyon bozukluğunun belirlenmesinde biyokimyasal belirteçlerin performansını ölçebilmede 'alıcı işlem karakteristikleri' (ROC) analizi yapıldı. Böbrek fonksiyon bozukluğunun göstergesi olarak Sistatin C > 1 mg/dL anlamlı kabul edildi ve Ca×P optimal kesme noktası 37,535 olarak bulundu. ROC eğrisi altında kalan alan 0,678 (p=0,002), sensitivite 0,573, spesifite 0,800 idi. Tüm olgularda Ca×P seviyeleri için median değeri 37,730 bulundu ve bu değer, kesim noktasına (37,535) çok yakındı. Kesim noktası değerine göre diyaliz gupları arasında CysC için anlamlı fark vardı. (p< 0.05) Çalışmamızda farklı tedavi şekillerine göre gruplandırılan tüm hastalarda Ca×P kritik değerinin ROC analizi sonuçlarına göre 37,535 olarak alınabileceğini görüldü. Serumda Ca, P ölçüm performansı yüksek parametreler olup, Ca×P çarpımı değerleri kolay elde edilebilir. Çalışmamızda bulduğumuz kritik değer, böbrek fonksiyon bozukluğunun tespiti ve kardiyovasküler komplikasyonları belirleme açısından ileri çalışmalarla teyit edilmelidir.

Anahtar kelimeler: *Böbrek fonksiyon bozukluğu, kalsiyum, fosfor, sistatin C*

INTRODUCTION

Chronic renal failure (CRF) and mineral bone disorder is a systemic disorder of mineral and bone metabolism that demonstrates either one, or a combination of, mineral metabolism abnormality, alteration of bone or extraskeletal calcification, occurring in patients with CRF (1). CRF and bone mineal disorder is caused by the initiation of mineral metabolism abnormality such as serum calcium (Ca), phosphorus (P), vitamin D3 (calcitriol) or parathyroid hormone (PTH) (2). Mineral metabolism abnormalities occur in early stage of CRF and increase of severity in advanced stage (3,4). Mortality risk increased to 10 to 61% in pre-dialysis and dialysis patients who had mineral metabolism abnormalities (5,6). The study, in 22,937 hemodialysis patients, indicated that patients who could not control all three clinical parameters (Ca, P and PTH levels) had a 51% significant increase of mortality risk compared to patients who could control all of three clinical parameters (7). The serum Ca, P, CaxP product and PTH achieved K/DOQI 2003 target recommendations in 40% to 90%, 50 to 90%, 70% to 99% and 10% to 49%, respectively (8). CRF patients, are at much higher risk of cardiovascular disease than the general population. High serum P and CaxP product levels play important role in pathogenesis of cardiovascular calcification and is a frequent and important role in pathogenesis of cardiovascular risk factor in patient with CRF (9). The ROC curve is a fundamental tool for diagnostic test evaluation. We aimed to compare the diagnostic performance of Ca×P product and to examine the critical value to differentiate the population with CRF arranged in groups for modality.

MATERIAL AND METHOD

Patient selection: CRF patients who did not require dialysis before (preD group, N=36), chronic renal disease patients on peritoneal dialysis (PD group, N=36), on hemodialysis treatment (HD group, N=35) and renal transplant patients that they had operation in three years. (Tx group, N=36), and also healthy individuals (control group, N=30) between 18 and 75 were included in the study (77 male, 96 female, totally N=173). The Ethical Committee had approved the study.

Age, gender, body mass index (BMI), presence of diabetes mellitus, hypertension, history of ischemic heart disease (IHD), smoking status, alcohol consumption, drugs administered were all recorded. (Table 2,3)

Laboratory analysis: Venous blood collection was performed at the beginning of HD or PD. Serum samples

***Table 1**. Descriptive statistics of calcium, phosphorus, CaX P, , PTH and CysC among groups[§]*

	Hemodialysis Group Mean±SD	Periton Dialysis Group Mean±SD	Predialysis Group Mean±SD	Transplantation Group Mean±SD	Control Group Mean±SD	F or KW	p
Calcium (mg/dl)	8.76±0.78	9.1±0.82	8.92±0.66	9.94±0.59	9.53±0.27	18.48	0.0001
Phosphorus (mg/dl)	5.57±1.25	5.32±1.57	4.46±0.83	3.03±0.65	3.57±0.63	36.91	0.0001
Ca×PO4	48.73±11.27	48.84±16.9	39.85±8.27	29.98±5.63	34.1±6.31	22.37	0.0001
PTH (pg/ml)	573.89±798.21	1029.49±973.84	339.91±206.11	106.23±77.68	65.11±32.07	189.9	<0.001
CysC (mg/dl)	3.58±2.39	6.20±1.37	5.87±1.13	1.33±0.28	0.72±0.12	14.60	0.001

[§]SD: Standard deviation, F: Test statistics for the one way analysis of variance (ANOVA),
KW: Test statistics for the Kruskal Wallis test, p: Statistical significance

for cycstatin C (CysC) were frozen at -80ºC. In routine practice, biochemical parameters including sodium (Na), Ca, P, PTH, CysC were measured in the medical biochemistry laboratory (Siemens Healthcare Diagnostics, USA). Their measurement procedure were appropriate kit inserts. When serum containing CysC is mixed with the latex particles coated with rabbit anti-cystatin C antibody, agglutination takes place resulting in an increase in turbidity. According to the kit insert (Siemens Healthcare Diagnostics, USA) the intra-assay and inter-assay precisions coefficient of variation (CV) were 1.0 and 1.8 % at a low level of 0.60 mg/L, and 1.8 and 3.1 % at a high level of 4.95 mg/L, respectively.

Statistical analysis: Mean ± standard deviation, median, minimum and maximum values are used as descriptive measures of continuous data. For the qualitative data, frequencies and percentages (%) are presented. Kolmogorov-Smirnov test is used to check the normality of data among groups. For normally distributed data One Way Analysis of Variance (with Tamhane's T2 multiple comparison test) is used for comparison of groups. For non-normally distributed data, Kruskal Wallis Analysis of Variance (with Conover multiple comparison test) is used for comparison of groups. Associations between categorical variables are assessed using the cross-tables and Chi-squared tests.

The ROC analysis is used to measure the performance of biochemical parameters in detecting kidney dysfunction. In the ROC analysis, the best cut-off value for biochemical parameters were defined as that which gave the highest sum of sensitivity and specificity. For all statistical analysis SPSS version 21.0 for Windows was used and the significance was set at $p<0.05$.

RESULTS

According to ANOVA test, there were significantly differences among groups for distrubitions of age and body mass index ($p<0.001$, $p< 0.025$, respectively). For categorical variables we used cross-tables and Chi-squared tests. At hemodialysis group smoking cigarettes were significantly higher than Tx and control groups. At all group, there were no statistical significant differences for alcohol, diabetes, hypertension and IHD ($p=0.757$, $p=0.220$, $p=0.159$, $p=0.152$ respectively).In this study, all groups Ca, P, CaxP product, PTH and CysC levels were measured . Results are given in Table 1. For Cys C , 1mg/ dL was a limitation of the system in healty individuals. We also detected, CysC>1 mg/dL in our all patient group (n=139), CysC<1 mg/dL in control group (n= 34). Because of secondary hyperparathroidism, all patients groups PTH were

***Table 2**. Distributions of age and body mass index (BMI) among groups[§]*

	Hemodialysis Group Mean±SD	Periton Dialysis Group Mean±SD	Predialysis Group Mean±SD	Transplantation Group Mean±SD	Control Group Mean±SD	F	p
Age (years)	52.00±15.46	51.19±9.76	54.64±9.37	40.14±13.08	36.53±11.43	14.8	<0.001
BMI (kg/m2)	24.11±5.00	24.95±4.20	27.33±4.85	26.51±5.82	27.44±5.64	1.86	0.025

[§]SD: Standard deviation, F: Test statistic for the one way analysis of variance (ANOVA), p: Statistical significance

***Table 3**. Distribution of smoking, alcohol, diabetes mellitus, hypertension, and ischemic coroner disease among groups*[§]

		Hemodialysis Group Freq.	%	Periton Dialysis Group Freq.	%	Predialysis Group Freq.	%	Transplantation Group Freq.	%	Control Group Freq.	%	
Smoking	Absent	20	57.10%	27	75.00%	27	75.00%	36	100.00%	26	86.70%	x^2:21,11
	Present	15	42.90%	9	25.00%	9	25.00%	0	0.00%	4	13.30%	p=0.0001
Alcohol	Absent	34	97.10%	35	97.20%	35	97.20%	36	100.00%	30	100.00%	x^2:1,88
	Present	1	2.90%	1	2.80%	1	2.80%	0	0.00%	0	0.00%	p=0.757
Diabetes	Absent	24	68.60%	25	69.40%	19	52.80%	27	75.00%	0	0.00%	x^2:4.41
Mellitus	Present	11	31.40%	11	30.60%	17	47.20%	9	25.00%	0	0.00%	p=0.220
HT	Absent	6	17.10%	9	25.00%	2	5.60%	7	19.40%	0	0.00%	x^2:5.17
	Present	29	82.90%	27	75.00%	34	94.40%	29	80.60%	0	0.00%	p=0.159
ICD	Absent	27	77.10%	28	77.80%	31	86.10%	34	94.40%	0	0.00%	x^2:5.28
	Present	8	22.90%	8	22.20%	5	13.90%	2	5.60%	0	0.00%	p=0.152

[§]Freq.: Frequency, %: Percentage, x^2: test statistic for the Chi-square analysis, p: Statistical significance.
At hemodialysis group smoking cigarettes were significant higher than transplantation and control group. At all group, there were no statistical significant differences for alcohol, diabetes , HT , and ICD . (p=0.757 ,p=0.220 ,p=0.159 ,p=0.152).

high and control groups were normal levels. ROC analysis, CaxP product was found to be successful in detecting renal dysfunction. Area under the ROC curve was 0.678, p=0.002, (Figure 1). The optimal cut-off value for CaxP product was obtained as 37.535 and the sensitivity and specificity was 0.573 and 0.800, respectively. Moreover, there was a significant difference in CysC between the two groups of dialysis according to cut-off value of 37.535 (p=0.05). Median value of all the groups for CaxP product was found as 37.730; very near the cut-off value (37.535) (Figure 1).

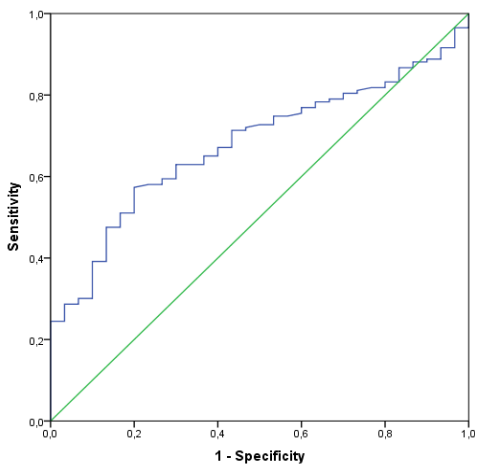

***Figure 1**. Receiver operating characteristics curve (ROC) of calcium phosphorus product in predicting renal dysfunction (AUC=0.678, p=0.002).*

DISCUSSION

Prevalence of cardiovascular disease is approximately 40% in hemodialysis patients. Apart from uremia related risk factors, hemodialysis treatment itself may play a role in the pathogenesis of coronary disease in uremic patients. The hemodialysis patients showed higher progression of coronary artery calcification scores associated with age, BMI and Framingham risk index (10).

Cystatin C does not appear to be affected by age, gender, or muscle mass, and there is evidence to suggest that it may be a more sensitive detector of incipient renal dysfunction than creatinine-based estimates of GFR such as the Cockroft-Gault or Modification of Diet in Renal Disease (MDRD) formulas. Several recent reports have indicated that CysC may be a better predictor of adverse cardiovascular events and all-cause mortality than either serum creatinine or creatinine-based estimating equations (11). It was reported that Ca×P showed a mortality risk trend similar to that seen with serum P alone. Those in the highest quintile of the Ca×P product (>72 mg2/dL2) had a relative mortality risk of 1.34 relative to those with products of 42 to 52 mg2/dL2 (12).

In a study describing the recent status, significant predictors, and potential consequences of abnormal mineral metabolism in representative groups of hemodialysis facilities (N=307) and patients (N=17,236) participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS); all-cause mortality was significantly and in-

dependently associated with serum concentrations of P (Relative Risk (RR) 1.04 per 1 mg/dL, P=0.0003), Ca (RR 1.10 per 1 mg/dL, P<0.0001), Ca×P product (RR 1.02 per 5 mg2/dL2, P=0.0001), PTH (1.01 per 100 pg/dL, P= 0.04), and dialysate Ca (RR 1.13 per 1 mEq/L, P=0.01). Cardiovascular mortality was significantly associated with the serum concentrations of P (RR 1.09, P < 0.0001), Ca (RR 1.14, P < 0.0001), Ca×P product (RR 1.05, P < 0.0001), and PTH (RR 1.02, P= 0.03). The adjusted rate of parathyroidectomy varied 4-fold across the DOPPS countries, and was significantly associated with baseline concentrations of P (RR 1.17, P < 0.0001), Ca (RR 1.58, P < 0.0001), Ca×P product (RR 1.11, P < 0.0001) (13).

A morbidity score (MORS) was created by scoring seventeen clinical, biochemical and radiological parameters as one or zero. In the group showing MORS < 5/17 (n=17) Ca×P was (46.53±14.44) significantly lower than the group MORS > 6/17 (n=17) Ca×P (55.99 ±19.31). And there was a positive correlation between MORS and Ca×P (14). In another study, the risk of morbidity was increased with Ca×P over 70 (15). In a study with 107 HD receiving individuals, patients were divided into 2 groups according to PTH levels; patients with PTH levels 4 or more times higher than the normal range had higher CaxP (55.6±18.2 mg2/dl2) than the patients with normal PTH levels (50.2±17.3 mg2/dl2; p>0.05). High levels of PTH are associated with diastolic dysfunction and left ventricular hypertrophy in HD patients, but there was no significant difference in ejection fraction rates between the groups (p>0.05) (16). It was previously recommended that serum CaxP product of patients with CRF should be less than 55 mg2/dL2. Achieving these more rigorous treatment goals will require a shift in the therapeutic management strategies to incorporate aggressive use (17). In the group dialysis performed with a blood flow rate of lower than 350 mL/min serum CaxP (51.00±8.95) and were PTH (302.1±160.02 pg/mL) levels significantly higher than the group with a blood flow rate equal to and higher than 350 mL/min (45.82 ± 4.87 mg2/dL2, 176.53 ± 51.73 pg/mL, p<0.05, p <0.01, respectively) (18).

Gromadzinski L. at all were found that hypocalcemia is an independent predictive factor for left ventricul diastolic dysfunction in patients with CRF. The area under the ROC curve of Ca for diastolic dysfunction was 0.627, 95 % CI (0.511-0.734), p=0.04, where as ROC deriveded Ca value of < 9.82 mg/ dL was characterized by a sensitivity of 91.8% and specifity of 38.1% for diagnosing complications in patients with CRF (19).

In our study, although Ca×P showed weak diagnostic performance (AUC=0.678), the critical value was (37.535) very similar to the median value of whole the group (37.730). Estimated sensitivity (true positivity through patient population) was 0.573, specificity was (wrong negativity through healthy subjects) 0.800. Because of using these levels at patient population, high specifity were important. (0.10 mg/L for CysC was a limitation of the measuring system in healthy individuals, according to the kit insert.)

We think that the recommended target of < 55 mg2/dL2 is needed to be revised to predict the extraskeletal calcification threatening the life span of the patient with CRF. Echocardiography findings and monitoring adverse cardiovascular events should be helpful in evaluation of the critical value of Ca×P related with cardiovascular risk.

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