Hypoalbuminemia, Poor Calcium-Phosphorus Control and High Transporter Peritoneal Characteristics – Three Important 10-Year Survival Predictors for Peritoneal Dialysis Patients

Hipoalbüminemi, Kötü Kalsiyum-Fosfor Kontrolü ve Yüksek Geçirgenlikli Periton Karakteri - Periton Diyalizi Hastalarında 10 Yıllık Sağkalımı Belirleyen 3 Önemli Faktör

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ABSTRACT

OBJECTIVE: Peritoneal transport characteristic is a potential survival predictor. In this study we evaluated the effect of transport characteristics on 10 year patient survival and compared its' impact with other possible survival predictors.

MATERIAL and METHODS: We included 75 CAPD patients who were followed in our center for at least 10 years after initiation of PD. Based on the standard peritoneal equilibration test, PD patients were divided into two transporter groups: Low / Low average (n:27) and High / High Average (n:48). Clinical and demographic data were collected from patient charts and impact of transporter characteristics and some other well-known survival predictors were studied.

RESULTS: 10 year PD survival rates were significantly lower in H/HA group (p:0.001). Atherosclerosis-related mortality rate was significantly higher in H/HA group (45.9% vs. 7.6%, p:0.043). Hypoalbuminemia, increased CaxP, chronic inflammation, H/HA transport status were independent predictors of PD and patient survival. Further analysis revealed that hypoalbuminemia (p:0.0001) and increased CaxP levels (p:0.0001) were the main predictors.

CONCLUSION: This study suggests that peritoneal transport status is an important survival predictor. However keeping the calcium and phosphorus levels in recommended ranges, and improving nutritional status still have more importance for lowering mortality rates of PD patients.

KEY WORDS: Hypoalbuminemia, Calcium-Phosphorus product, High transporter peritoneum, Survival predictors, Peritoneal dialysis

ÖZ

AMAÇ: Periton geçirgenlik özellikleri potansiyel bir sağkalım prediktörüdür. Bu çalışmada geçirgenlik karakteri dahil olmak üzere bazı olası sağkalım prediktörlerinin PD hastalarının 10 yıllık sağkalımı üzerindeki etkileri araştırılmıştır.

GEREÇ ve YÖNTEMLER: Çalışmaya PD tedavisinin başından bu yana merkezimizde takip edilmekte olan 75 hasta dahil edilmiştir. Hastalar standart PET testine göre düşük/düşük-orta (n:27) ve yüksek/yüksek-orta (n: 48) geçirgenlikli gruplarına bölünmüştür. Klinik ve demografik özellikler hasta kayıtlarından toplanarak sağkalım üzerinde etkili olabilecek faktörler analiz edilmiştir.

BULGULAR: Yüksek geçirgenlik grubunda 10 yıllık hasta sağkalımı belirgin olarak düşüktür (p:0,001). Bu grupta ateroskleroza bağlı mortalite oranları da belirgin olarak yüksektir (%45,9 ve %7.6, p:0,043). Hipoalbüminemi, artmış CaxP, kronik inflamasyon ve yüksek geçirgenlik bağımsız PD ve hasta sağkalım prediktörü olarak saptanmışlardır. İleri analizdeyse Hipoalbüminemi (p:0,0001) ve artmış CaxP seviyeleri (p:0,0001) ana faktörler olarak görülmektedir.

SONUÇ: Bu çalışma periton geçirgenlik karakterinin önemli bir sağkalım prediktörü olduğunu göstermekle beraber beslenme durumunun düzeltilmesi ve kalsiyum-fosfor hedeflerine ulaşılması halen önemini koruyan faktörlerdir.

ANAHTAR SÖZCÜKLER: Hipoalbüminemi, Kalsiyum-fosfor çarpımı, Yüksek geçirgenlikli periton, Sağkalım prediktörleri, Periton diyalizi

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INTRODUCTION

Patients with end-stage renal disease (ESRD) have increased risk of premature death usually due to atherosclerosis-related diseases or infectious complications (1). Dialysis modality might also have some impact on this risk (2). Peritoneal dialysis (PD) patients' peritoneal transport characteristics (PTC) were also speculated to modify the well-known mortality risk factors like hyperlipidemia, malnutrition/hypoalbuminemia and chronic inflammation (3-5). PTC are defined by a peritoneal equilibration test (PET) which was standardized by Twardowski et al (6). PD regimens are arranged according to PET which is also an useful tool for patient follow-up and diagnosis of peritoneal dysfunctions. In our recent study we analyzed 84 PD patients who were receiving PD for minimum 36 months and found that high (H) and high-average (HA) transporter peritoneal membrane characteristics were risk factors for chronic inflammatory state (5). A comparison between transport groups revealed that the H/HA PTC was associated with lower albumin, higher C-reactive protein (CRP) levels, and higher recombinant human erythropoietin (rHuEPO) needs in the first 3 years of PD when compared with the L/LA type. Also percentage of patients who had an atherosclerosis-related event was significantly higher in H/HA group (43.1% vs. 18.1%, $p < 0.01$). We also reported that D/P creatinine levels were in positive correlation with CRP levels, and in negative correlation with mean albumin levels. In this current study we aimed to analyze the effects of some clinical characteristics on 10-year patient and PD survival.

MATERIAL and METHODS

After the publication of previous study, 7 patients underwent kidney transplantation and 2 patients moved to another center (5). All analyzes were performed after excluding these patients. Remaining study group size was 75 patients.

All patients were under CAPD and were receiving PD solutions (2000-2500 mL, glucose 1.36%, 2.27% or 3.86%, Baxter-Dianeal 137, Deerfield IL) four to five times daily. The weekly-calculated Kt/V value was 2.0 ± 0.3 during the follow-up period. PTC were identified after a PET at the third month of CAPD using the Dialysate/Plasma (D/P) reference values defined by Twardowski et al (4). Patients were classified according to one of four peritoneal transport types: high (H), high-average (H/HA), low (L) and low-average (LA). Then the patients were grouped as follows; H/HA, n:48 and L/LA, n: 27 patients.

Patient charts for 10 years from the beginning of PD were retrospectively investigated for monthly creatinine, albumin, CRP, hemoglobin (Hb), total cholesterol, triglyceride, calcium, phosphorus, intact parathyroid hormone (iPTH) levels. A mean value for each parameter was recorded as "mean follow-up value" for statistical analysis. Same data at the third month of dialysis were recorded as "initial values". Patient history (etiology for dropouts and mortality) was also collected. Atherosclerosis-related mortality was defined as mortality due to myocardial infarction, peripheral artery disease or atherosclerotic cerebrovascular event.

Statistical Analysis

Statistical analyses were performed by using the SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc, Chicago, IL, USA). Normality of data was analyzed by using a Kolmogorov-Smirnov test. All numerical variables with normal distribution were expressed as the means ± standard deviations (SD), while variables with skew distribution were expressed as medians and interquartile range (IR). Categorical variables were expressed as percentages and compared by chi-square test. Normally distributed numeric variables were analyzed by independent samples t-test and skew distributed numeric variables were compared using the Mann-Whitney U test. Survival analysis was performed by using the Kaplan-Meier and Cox-regression survival tests. A p-value < 0.05 was considered as statistically significant.

RESULTS

There was no significant difference in means of demographic and clinical characteristics of patient groups at the initiation of PD treatment (Table I). 20 out of 75 patients were alive and still on CAPD treatment at the end of the 10-year follow-up period [H/HA; 7 patients, 14.6% and L/LA; 13 patients, 48.1%, p:0.002, Table II). 12 patients were converted to the hemodialysis modality (H/HA; 11, 22.9%, L/LA; 1, 3.7%, p: 0.029). Reasons for conversion were as follows: H/HA group, insufficient ultrafiltration (n:3), peritonitis (n:8, 1 fungal peritonitis, 1 tuberculosis peritonitis), 1 L/LA patient converted to hemodialysis due to peritonitis. According to Kaplan-Meier survival analysis, overall 10-year PD survival rates (including mortality and conversion to HD) were significantly lower in the H/HA group (Figure 1, p:0.001). After excluding patients who converted dialysis modality, patient survival was still lower in H/HA group at the end of 10 years follow-up period (Figure 2, p:0.004). Causes of mortality were as follows; atherosclerosis-related (coronary or cerebrovascular mortality, H/HA; 17/30 patients, L/LA; 2/13 patients), infection-related (peritonitis or other infections, septicemia, H/HA; 12/30 patients, L/LA; 10/13 patients) and colon perforation (H/HA; 1/30 patient, L/LA; 1/13 patient). Atherosclerosis-related mortality rate was significantly higher in H/HA group (45.9% vs. 7.6%, p: 0.043, Figure 3).

Mean albumin levels were significantly higher in L/LA group (3.63 ± 0.32 vs. 3.42 ± 0.42 g/dL, p:0.026) while there was no significant difference in means of CRP levels [13.3 (12.7) vs. 10 (14) mg/L, p: 0.834]. Percentage of patients with mean albumin level ≤ 3.5 g/dL was also higher in H/HA group [n: 26 (54.2%) vs. n:8 (29.6%), p:0.04, Table II]. Percentage of patients with chronic inflammation (mean CRP level > 10 mg/L) were similar (n:27/48, 56.3% vs. n:14/27, 51.9%, p: 0.713). Other follow-up biochemical parameters were similar (Table II).

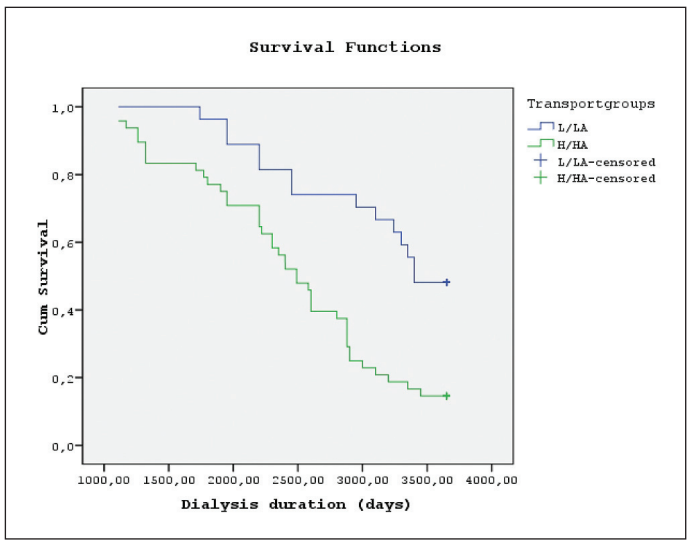

Figure 1: *PD survival is significantly lower in patients with H/HA peritoneal transport characteristic in 10 years follow-up period (p: 0.001)*

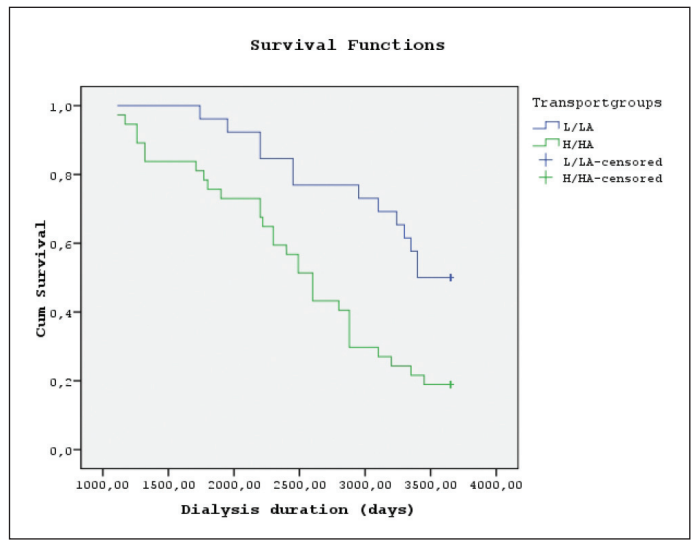

Figure 2: *10 years mortality rates were significantly higher in patients with H/HA peritoneal transport characteristic after excluding patients whom converted dialysis modality to hemodialysis (p: 0.004)*

Table I: Comparison of initial characteristics (3rd month on PD) of H/HA and L/LA patients.

Mean ± SD, Median (IR)	**H/HA Group (n:48)**	**L/LA Group (n:27)**	**p value**
Age (y)	44.0 ± 15.6	46.4 ± 16.4	0.684
Gender (M/F)	22/26	18/9	0.083
Albumin (g/dL)	3.27 ± 0.49	3.38 ± 0.41	0.167
C-reactive protein (mg/L)	12.5 (19)	10 (20.5)	0.407
Ferritin (ng/mL)	300 (476.2)	414.6 (825)	0.092
Hemoglobin (g/dL)	9.6 ± 1.3	10.1 ± 1.5	0.171
Intact parathyroid hormone (pg/mL)	150 (200)	105 (349)	0.779
Total cholesterol (mg/dL)	182.3 ± 47.3	188.6 ± 44.3	0.861
Triglyceride (mg/dL)	129 (95)	156 (102.5)	0.216
Creatinine (mg/dL)	6.7 ± 1.4	6.1 ± 1.9	0.084
Corrected Calcium (mg/dL)	9.13 ± 0.48	8.92 ± 0.53	0.094
Phosphorus (mg/dL)	4.89 ± 1.18	4.88 ± 1.15	0.980
Etiologies for ESRD (n)			
Diabetic nephropathy	5	3	0.542
Hypertensive nephropathy	9	4	
Primary glomerulonephritis	9	4	
Polycystic kidney disease	8	4	
Chronic tubulointerstitial disease	17	9	
Unknown	-	3	

A Cox regression analysis revealed that hypoalbuminemia (< 3.5 g/dL), increased CaxP product levels (> 55), chronic inflammation, H/HA peritoneal transport status were independent predictors of overall PD survival (including mortality and conversion to HD, Table III). However, further analysis revealed that hypoalbuminemia (p: 0.0001) and increased Ca x P levels (p: 0.0001) were the main survival predictors.

Table II: Comparison of 10 year followed-up period mean values of H/HA and L/LA patients.

Mean ± SD, Median (IR)	H/HA Group (n:48)	L/LA Group (n:27)	p value
Albumin (g/dL)	3.42 ± 0.42	3.63 ± 0.32	0.026
Hypoalbuminemia frequency (n, %)	26, 54.2%	8, 29.6%	0.04
C-reactive protein (mg/L)	13.3 (12.7)	10 (14)	0.834
Chronic inflammation frequency (n, %)	27, 56.3%	14, 51.9%	0.713
Ferritin (ng/mL)	350 (363)	460 (530)	0.187
Hemoglobin (g/dL)	10.7 ± 1.4	10.9 ± 1.2	0.674
Intact parathyroid hormone (pg/mL)	165.5 (414)	258 (425)	0.886
Total cholesterol (mg/dL)	175.9 ± 42.7	188.2 ±67.8	0.137
Triglyceride (mg/dL)	129 (131)	145 (99)	0.453
Creatinine (mg/dL)	7.14 ± 1.56	6.56 ± 1.65	0.145
Corrected Calcium (mg/dL)	9.15 ± 0.76	8.93 ± 0.71	0.229
Phosphorus (mg/dL)	4.63 ± 1.22	4.05 ± 1.23	0.51
Ca x P product	42.1 ± 10.3	36.1 ± 11.1	0.21
Number of patients with Ca x P > 55 (n, %)	9, 18.8%	2, 7.4%	0.183
Dialysis modality conversion rates (n, %)	11, 22.9%	1, 3.7%	0.029
Insufficient ultrafiltration Peritonitis Fungal peritonitis Tuberculosis peritonitis	3 6 1 1	- 1 - -	
Mortality rates (n, %)	30, 81%	13, 50%	0.002
Atherosclerosis related Infection related Colon perforation	17 12 1	2 10 1	0.043

Table III: Independent predictors of patient survival (Cox Multivariate Analysis).

Variable	β	SE	Exp (β)	p value
H/HA transporter	0.780	0.389	2.182	0.045
Chronic inflammation (CRP > 10 mg/L)	0.805	0.421	2.237	0.027
Serum albumin < 3.5 g/dL	1.579	0.421	4.852	0.0001
Ca x P > 55	1.874	0.519	6.516	0.0001
Age at dialysis initiation > 55 years	0.453	0.357	1.572	0.204
iPTH levels (mean iPTH > 600 or < 100 pg/mL)	0.126	0.354	1.135	0.722
Anemia (Mean Hemoglobin < 10 g/dL)	0.198	0.403	1.219	0.623

DISCUSSION

In this study we found that H/HA PTC is associated with decreased PD and patient survival in 10 years follow-up period. Main reasons of PD to HD conversion were insufficient ultrafiltration and peritonitis-related complications in H/HA group. Atherosclerosis-related mortality was also significantly higher in H/HA patients. We also found that H/HA patients had lower albumin levels and hypoalbuminemia (< 3.5 g/dL) was also more frequent in these patients. There was a tendency for hyperphosphatemia and increased CaxP product levels in the

H/HA group compared to L/LA patients but without statistical significance (Table II). A regression analysis revealed that H/HA PTC has a significant negative impact on survival with hypoalbuminemia, increased CaxP and chronic inflammation.

Survival of ESRD patients is significantly lower than normal population. Factors associated with increased mortality were extensively studied by nephrologists and some significant factors like chronic inflammation, hypoalbuminemia with/without clinical malnutrition, hyperphosphatemia, increased CaxP product levels, severe anemia are already defined as factors associated with all-cause and atherosclerosis-related mortality (5, 7-12). The preferred dialysis modality might also have an effect on mortality risk as some complications are known to be associated with only HD while some with only PD such as central venous catheter infections and sclerosing peritonitis respectively. PTC is one of these modality-specific conditions that might have an impact on survival rates of PD patients (13-17).

The PTC, which is defined by a standardized PET at the initiation of PD, gives the clinician important data that affect PD modality choice and also provides a clue about possible complications that can be seen in the patient during the follow-up period (6). The H/HA characteristic is associated with increased clearance but also with decreased ultrafiltration rates while the L/LA characteristic is associated with excellent ultrafiltration but low dialysis efficiency. Guidelines encourage clinicians to use HD (in patients with high body surface area) or high dose CAPD in L/LA to increase low clearance rates. On the other hand to increase ultrafiltration rates; an automated PD device (APD) is usually advised in H/HA patients. Despite increased UF rates with APD, H/HA patients are still under risk of hypoalbuminemia and protein malnutrition due to increased peritoneal protein clearance (5, 15).

Supporting our findings, in the CANUSA study, Churchill et al. reported that the 2-year patient survival probabilities were 91%, 80%, 72% and 71 % for L, LA, H and HA groups, respectively (15). Similarly, in a meta-analysis, Brimble et al. reported that high transport status is associated with increased mortality rates (16). Rumsfeld et al. analyzed survival in 5170 PD patients and reported that high PTC is a highly significant and an independent risk factor for mortality (17).

The exact mechanisms for the poorer survival of H/HA transporters remain unclear. This might be a result of an increased albumin loss, hypoalbuminemia, low ultrafiltration rates, chronic inflammation and increased oxidative stress (15-18). Malnutrition and hypoalbuminemia are already well known complications of H/HA transport status (5). Two most possible explanations for higher malnutrition rates are increased absorption of glucose from dialysis fluid, leading to suppression of appetite, and increased protein losses. In our recent study we reported that H/HA transport status was associated with lower albumin levels when compared to L/LA type (5). Several studies also have reported that low serum albumin is a predictor of mortality in CAPD population (9-11). In the current study we found that hypoalbuminemia (<3.5 mg/dl) was significantly more frequent in the H/HA group and serum albumin levels were one of the main predictors of PD survival with increased CaxP product levels. Low serum albumin usually reflects poor nutritional status and underlying chronic inflammation; one should therefore be extra careful about the nutritional support of these patients.

In stage 5 chronic kidney disease patients, high levels of plasma calcium, serum phosphate, and iPTH play a critical role in the pathogenesis of cardiovascular events (19) and the mechanism underlying this cardiovascular risk appears to be a direct effect of arterial calcification. There is strong evidence that vascular calcification is closely associated with high serum Ca and P levels and a high serum Ca x P product (20). According to our findings there was no significant difference between groups in means of Ca, P and CaxP levels. However all 11 patients (9 in H/HA group) who had a mean CaxP level > 55 lost their lives due to atherosclerosis-related events, in conformance with previous reports (19, 20).

In current study, we found that the atherosclerosis-related mortality rate was higher in H/HA group than L/LA group (45.9% vs. 7.6%, p: 0.043, Figure-3). It has already been reported that volume expansion and patients with symptomatic fluid retention are more likely to be high than low transporter (7, 8, 15). Consequently, this higher mortality rate might be due to excess overhydration in the H/HA group. The malnutrition-inflammation-atherosclerosis complex syndrome (MICS) is another well-defined risk factor for mortality in ESRD patients. In MICS there is a tendency of concurrence of malnutrition, hypoalbuminemia and chronic inflammation,

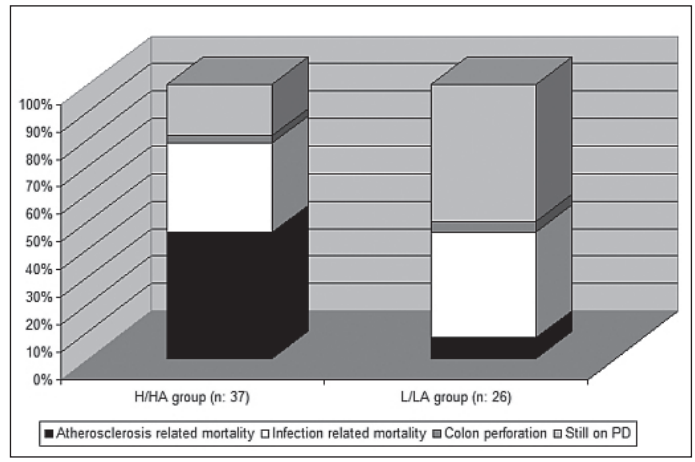

Figure 3: *Mortality rates were significantly higher in H/HA group (p: 0.002). Atherosclerosis related mortality was significantly more prevalent in H/HA group (45.9% vs 7.6%, p: 0.043).*

all factors increasing risk for atherosclerosis-related mortality. In our previous study we found that chronic inflammation and hypoalbuminemia were more frequent in the H/HA group in the first 3-year follow-up period (5). In this study we also found both conditions still continue in the H/HA group in the 10-year follow-up period and both have an important impact on mortality rates along with transport characteristic (Table II, III).

In conclusion, this study suggests that H/HA transporters have a significant survival disadvantage due to direct and indirect effects of PTC on well known mortality risk factors like hypoalbuminemia and chronic inflammation. Despite these findings, hypoalbuminemia and increased CaxP levels seem to be the major survival predictors. Based on these findings, we suggest that H/HA patients should be under close follow-up for hypoalbuminemia, malnutrition, hypervolemia and atherosclerosis-related diseases and these comorbidities should be treated in early stages for better patient survival.

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