

Does Peritoneal Membrane Transport Affect Peritoneal Clearance of Beta 2–Microglobulin in Peritoneal Dialysis Patients?

Periton Diyalizi Hastalarında Periton Membran Transportu Beta-2 Mikroglobülinin Periton Klirensini Etkiler mi?

ABSTRACT

OBJECTIVE: Our aim in this study was to compare peritoneal clearance of beta 2-microglobulin (B2M) in peritoneal dialysis (PD) patients who had high and low membrane transport status.

MATERIAL and METHODS: Forty-nine PD patients were included in this study. The patients were divided into two groups according to their peritoneal equilibration test (PET) results; high transport group and low transport group. Serum B2M levels and peritoneal clearance of B2M were compared between the two groups.

RESULTS: Dialysate B2M level and peritoneal clearance of B2M were higher in the high transporter group than in the low transporter group (5.92 ± 2.62 mg/L vs. 3.42 ± 1.51 mg/L, $p: <0.001$ and 11.13 ± 2.14 L/week/1.73 m² vs. 6.41 ± 1.65 L/week/1.73 m², $p: <0.001$, respectively). On the other hand, there was no significant difference in serum B2M concentration between the high transport group and the low transport group (24.15 ± 9.10 mg/L vs. 27.35 ± 10.10 mg/L, respectively, $P>0.05$). Serum B2M concentration was positively correlated with duration of PD ($r: 0.518$, $p: <0.001$).

CONCLUSION: Although dialysate levels and peritoneal clearance of the middle molecule B2M were significantly higher in high transporters compared to low transporters, there was no significant difference between the two groups in terms of serum B2M concentration.

KEY WORDS: Beta-2 microglobulin, High transporter, Low transporter, Middle molecule, Peritoneal clearance

ÖZ

AMAÇ: Bu çalışmada, yüksek ve düşük geçirgen membran transport özelliğine sahip periton diyalizi (PD) hastalarında beta 2-mikroglobülinin (B2M) periton klirenslerini karşılaştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: Kırk dokuz PD hastası çalışmaya alındı. Hastalar periton eşitleme testi (PET) sonuçlarına göre iki gruba ayrıldı; yüksek geçirgen grup ve düşük geçirgen grup. İki grup arasında serum B2M düzeyleri ve B2M'nin periton klirensleri karşılaştırıldı.

BULGULAR: Diyalizat B2M düzeyi ve B2M'nin periton klirensleri yüksek geçirgen grupta düşük geçirgen gruba kıyasla daha yüksekti (sırasıyla 5.92 ± 2.62 mg/L'ye karşın 3.42 ± 1.51 mg/L, $p: <0.001$ ve 11.13 ± 2.14 L/hafta/1.73 m² vs. 6.41 ± 1.65 , L/hafta/1.73 m², $p: <0.001$). Öte yandan yüksek geçirgen grup ile düşük geçirgen grup arasında serum B2M konsantrasyonu açısından anlamlı fark saptanmadı (sırasıyla 24.15 ± 9.10 mg/L'ye karşın 27.35 ± 10.10 mg/L, $P>0.05$). Serum B2M konsantrasyonu PD süresi ile ilişkiliydi ($r: 0.518$, $p: <0.001$).

SONUÇ: Orta molekül ağırlıklı molekül olan B2M'nin diyalizat düzeyleri ve periton klirensleri yüksek geçirgenlerde düşük geçirgenlere kıyasla anlamlı olarak daha yüksek olmasına rağmen, serum B2M konsantrasyonu açısından iki grup arasında anlamlı fark yoktu.

ANAHTAR SÖZCÜKLER: Beta 2-mikroglobulin, Yüksek geçirgen, Düşük geçirgen, Orta molekül Ağırlıklı molekül, Periton klirensi

Mesut AKÇAKAYA
Oktay OYMAK
Feridun KAVUNCUOĞLU
Aydın ÜNAL
Bülent TOKGÖZ
Cengiz UTAŞ

Erciyes University, Faculty of Medicine,
Department of Nephrology,
Kayseri, Turkey

Received : 21.03.2012

Accepted : 16.07.2012

Correspondence Address:

Aydın ÜNAL
Erciyes Üniversitesi Tıp Fakültesi,
Nefroloji Bilim Dalı, Kayseri, Turkey
Phone : +90 352 437 93 49
E-mail : aydinunal2003@gmail.com

INTRODUCTION

Beta 2-microglobulin (B2M), a prototype of middle-molecule uremic toxins, is a low molecular weight protein (11800 Da), which is produced by all cells expressing the major histocompatibility class I antigens. Under physiological conditions, B2M is generated at a constant rate, except in patients with systemic inflammation and haematopoietic neoplasia (1).

It is produced at 150-200 mg per day and eliminated from the circulation through the renal pathway (2). B2M is filtered by the glomerulus and is degenerated in the proximal tubules through a megalin-dependent pathway (3). Circulating B2M levels are elevated in patients with a reduced glomerular filtration rate (GFR). In dialysis patients, in whom GFR is almost completely abolished, B2M accumulates in the circulation. Although it remains unknown whether the B2M molecule itself is a uremic toxin, B2M has been considered to be a surrogate marker of putative middle-molecule uremic toxins, which are difficult to dialyze by use of a low flux membrane (4). It has been demonstrated that elevated concentration of circulating B2M is a potential risk for the development of dialysis-related amyloidosis (5). Advanced glycosylation end product (AGE) may affect the pathophysiological impact of B2M. AGE-modified B2M has been identified in amyloid deposits in hemodialysis (HD) patients (6). AGE also enhances monocyte migration and cytokine secretion (7), suggesting that AGE-B2M may initiate an inflammatory response, leading to bone/joint destruction (6-7).

It has been reported that serum B2M levels are lower in peritoneal dialysis (PD) patients than in HD patients [8]. This may be due to better conservation of residual renal function with PD, because PD alone poorly clears B2M [9]. Several methods to reduce plasma B2M levels including the use of high-flux membrane, ultrapure dialysate [4], hemodiafiltration [10-11], and the absorptive affinity column for B2M [5] have been attempted in dialysis patients. Peritoneal clearance of B2M and serum B2M levels in PD patients was evaluated in a few studies. Our aim in this study was to compare serum B2M levels and peritoneal clearance of B2M in PD patients who had high and low membrane transport status.

MATERIAL and METHODS

This study was performed at the Department of Nephrology, Erciyes University Medical School between January 2007 and December 2008. Forty-nine (25 males and 24 females) PD patients were included in this study. Thirty-eight of 49 patients were on continuous ambulatory peritoneal dialysis and the rest were on automated peritoneal dialysis. Patients who had acute illness, significant infection or malignancy, were excluded from the study. The study protocol was approved by the local ethics committee. The study procedures were approved by all patients.

The peritoneal equilibration test (PET) was performed in all

patients. Peritoneal transport of creatinine was measured using a 4-hour sample during standardized PET (12). Because the number of patients was low, the patients were divided into two groups according to their PET results; high transport group (n: 25; only high) and low transport group [n: 24 (14 low; 10 low average)].

Serum albumin, glucose, blood urea nitrogen, and creatinine and dialysate creatinine and glucose were measured by using routine laboratory methods.

Dialysate B2M level was measured with 4-hour samples during PET. The serum B2M level was also evaluated concurrently. The serum and dialysate B2M levels were determined with Beckman Coulter Immage Nephelometry system (Fullerton, CA).

PD dialysate samples for a period of 24 hours were obtained and dialysate urea, creatinine, and B2M clearances were calculated. All clearances were normalized to 1.73 m² of body surface area (BSA).

Anuria was defined as 24-h urine output < 100 mL and/or residual GFR < 1 mL/min. Five of the 49 PD patients were anuric. Among the anuric patients 3 were high transporter and 2 were low transporter.

Peritoneal, renal, and total Kt/Vurea were calculated according to National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (13).

Statistical Analysis

Statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS) 15.0 for Windows. The Kolmogorov-Smirnov test was used to determine normality of distributions of variables. Continuous variables with normal distribution are presented as mean $\pm$ standard deviation. The median value was used where normal distribution was absent. Statistical analysis for the parametric variables was performed using the Student's t-test between two groups. The Mann-Whitney U test was used to compare nonparametric variables between two groups. The correlation analysis was evaluated by Spearman's correlation test for nonparametric variables. Qualitative variables are given as percent and the correlation between categorical variables was investigated using the chi-square test and Fisher's exact test. A p value of <0.05 was considered significant.

RESULTS

The etiology of end-stage renal disease (ESRD) was hypertension in 18 (36.7%), diabetes mellitus in 11 (22.4%), nephrolithiasis in 2 (4.1%), amyloidosis in 2 (4.1%), glomerulonephritis in 1 (2.0%), polycystic kidney disease in 1 (2.0%), and others/unknown in 14 (28.6%).

Demographic and clinical findings of the patients are shown in Table I. There was no significant difference between two

Table I: Demographic and clinical findings of the patients.

Parameter	High transporter (n: 25)	Low transporter (n: 24)	P value
Age (years)	50.96 ± 14.76	44.58 ± 16.97	0.167
Male/female	15/10	10/14	0.159
Weight (kg)	66.00 ± 15.26	65.20 ± 13.29	0.844
Body surface area (m2)	1.70 ± 0.21	1.70 ± 0.19	0.897
PD duration (month)	28 (3-131)	34 (1-132)	0.522
24-h urine output (mL)	1261 ± 660	924 ± 719	0.168
Etiology of ESRD			0.533
Hypertension	9	9	
Diabetes mellitus	7	4	
Nephrolithiasis	1	1	
Amyloidosis	2	-	
Glomerulonephritis	-	1	
Polycystic kidney disease	-	1	
Others/unknown	6	8	

PD: peritoneal dialysis, **ESRD:** end-stage renal disease

Table II: Comparison of biochemical findings between high transporters and low transporters.

Parameter	High transporter (n: 25)	Low transporter (n: 24)	P value
Serum albumin (g/dL)	2.66 ± 0.64	3.17 ± 0.45	0.003
Serum B2M (mg/L)	24.1 ± 9.10	27.55 ± 10.10	0.248
Dialysate B2M (mg/L)	5.92 ± 2.62	3.42 ± 1.51	<0.001
Gradient of B2M*	18.23 ± 7.86	23.93 ± 8.98	0.022
Total Kt/Vurea	2.75 ± 0.83	2.57 ± 0.59	0.376
Peritoneal clearance of			
creatinine (L/week/1.73m ²)	55.58 ± 9.63	50.17 ± 6.48	0.026
urea (L/week/1.73m ²)	64.22 ± 14.03	66.87 ± 8.02	0.420
B2M (L/week/1.73m ²)	11.13 ± 2.14	6.41 ± 1.65	<0.001
B2M: Beta-2 microglobulin			

* Gradient of B2M denotes a gap between serum and dialysate B2M levels at 4-hour sample during the peritoneal equilibration test

groups with regard to age, gender, weight, BSA, duration of PD, 24-h urine output, and underlying renal disease ($p>0.05$). Table II demonstrates comparison of biochemical findings between high transporters and low transporters. Serum albumin level and gradient of B2M, which denotes a gap between serum and dialysate B2M levels at 4-hour samples during the PET, were

significantly lower in high transporters than in low transporters. On the other hand, dialysate B2M level and peritoneal clearance of creatinine and B2M were significantly lower in low transporters than in high transporters. There was no significant difference between two groups with regard to serum B2M level, total Kt/Vurea value, and peritoneal clearance of urea.

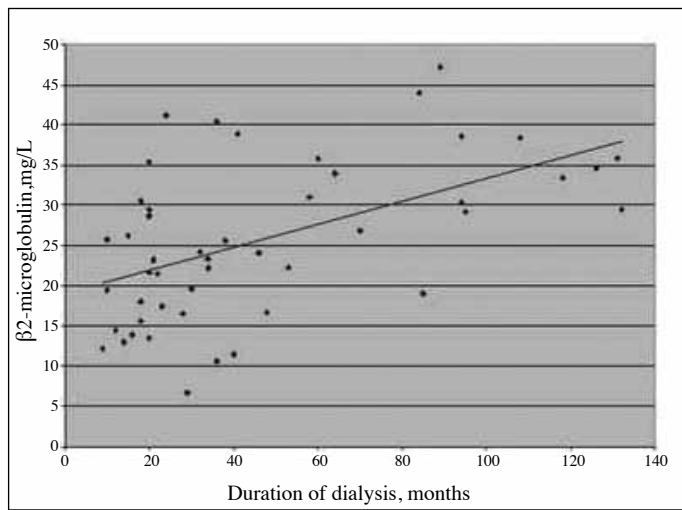


Figure 1: Relationship between serum beta 2-microglobulin concentrations and duration of peritoneal dialysis.

Serum B2M concentration was positively correlated with duration of PD ($r: 0.518$, $p: <0.001$, see Figure 1).

DISCUSSION

We found that serum B2M concentrations were positively correlated with duration of PD in PD patients. Serum B2M concentrations increased as the PD duration increased. Increase in serum B2M levels with PD duration and inverse correlation between residual renal function and serum B2M concentrations have also been reported in PD patients (14, 15). Some studies have demonstrated lower serum B2M concentrations in PD patients compared to HD patients, which is mainly explained by better preservation of residual renal function in PD patients (16-17). A progressive decline of residual renal function was responsible for increases in serum B2M concentration, because increased peritoneal clearance could not compensate the decreased renal clearance (18).

Serum B2M concentration was found to be lower in the high transporter group than the low transporter group (24.10 mg/L versus 27.55 mg/L) in the present study but this difference was not statistically significant. In contrast to our findings, Yamamoto et al. reported that the serum B2M concentrations were significantly higher in high and high average transporters than low and low average transporters in 12 anuric PD patients (14). Brophy et al. and Kim et al. demonstrated that peritoneal clearance of middle molecules such as B2M depends mainly on the total dwell hours of PD and not on the number of exchanges of dialysate (19,20). Yamamoto et al. reported that high peritoneal clearance of small molecules did not result in lower serum B2M concentrations especially in anuric patients and that the contribution of residual renal function to removal of B2M was more important than the contribution of peritoneal clearance

(14). In our study, we found that dialysate B2M concentration and peritoneal clearance of B2M were significantly higher in high transporters than in low transporters. Individual patient peritoneal membrane transport characteristics are important in determining total solute clearance and ultrafiltration rates in PD patients. High transporters tend to optimize both solute clearance and ultrafiltration after a short dwell time (21) but they are less successful in the removal of middle molecules. Although they would easily reach total solute clearance goals, it has recently been shown that these patients have an increased relative risk of death and a decreased technique survival (22).

Although there was no significant difference, serum B2M level was lower in high transporters than in low transporters. However, the dialysate B2M level was significantly higher in high transporters than in low transporters. On the other hand, the gradient of B2M was significantly higher in low transporters than in high transporters. These observations indicate that peritoneal B2M permeability increases if peritoneal permeability increases and supports the finding that dialysate B2M levels were significantly higher in high transporters than in low transporters.

There were some limitations of the present study. Firstly, the results were based on a small number of patients, and our findings should be validated with further studies. Secondly, it is possible that we could not fully control for all confounding variables which affect production and clearance of B2M. In addition, the influence of B2M and peritoneal clearance of B2M on morbidity and mortality should be examined in PD patients in future studies.

In conclusion, we demonstrated that dialysate B2M concentration and peritoneal clearance of B2M were higher in high transporters than low transporters in the present study. However, this increased peritoneal clearance of B2M in the high transporter PD group lead only to statistically insignificantly lower serum levels of B2M compared to the low transporter PD group.

REFERENCES

1. Okuno S, Ishimura E, Kohno K, Fujino-Katoh Y, Maeno Y, Yamakawa T, Inaba M, Nishizawa Y: Serum beta2-microglobulin level is a significant predictor of mortality in maintenance haemodialysis patients. *Nephrol Dial Transplant* 2009; 24: 571-577
2. Karlsson FA: Physical-chemical properties of beta 2-microglobulin. *Immunochemistry* 1974; 11: 111-114
3. Orlando RA, Rader K, Authier F, Yamazaki H, Posner BI, Bergeron JJ, Farquhar MG: Megalin is an endocytic receptor for insulin. *J Am Soc Nephrol* 1998; 9: 1759-1766
4. Lonneman G, Koch KM: Beta (2)-microglobulin amyloidosis: effects of ultrapure dialysate and dialyzer membrane. *J Am Soc Nephrol* 2002; 13(suppl1): S72-S77

5. Kazama JJ, Maruyama H, Gejyo F: Reduction of circulating beta2-microglobulin level for the treatment of dialysis related amyloidosis. *Nephrol Dial Transplant* 2001; 16 (Suppl 4): 31-35
6. Niwa T, Sato M, Katsuzaki T, Tomoo T, Miyazaki T, Tatemichi N, Takei Y, Kondo T: Amyloid beta2-microglobulin is modified with N epsilon-(carboxymethyl) lysine in dialysis related amyloidosis. *Kidney Int* 1996; 50: 1303-1309
7. Miyata T, Inagi R, Iida Y, Sato M, Yamada N, Oda O, Maeda K, Seo H: Involvement of beta2-microglobulin modified with advanced glycation and products in the pathogenesis of hemodialysis-associated amyloidosis. *J Clin Invest* 1994; 93: 521-528
8. Assounga A, Canaud B, Flavier JL, Slingeneyer A, Robinet-Lévy M, Aznar R, Mion C: What does circulating beta2-microglobulin signify in uremic patients on maintenance dialysis? *Nephrologie* 1987; 8: 301-306
9. Evenepoel P, Bammens B, Verbeke K, Vanrenterghem Y: Superior dialytic clearance of beta2-microglobulin and P-cresol by high-flux hemodialysis as compared to peritoneal dialysis. *Kidney Int* 2006; 70: 794-799
10. Bolasco P, Altieri P, Andrulli S, Basile C, Di Filippo S, Feriani M, Pedrini L, Santoro A, Zoccali C, Sau G, Locatelli F: Convection versus diffusion in dialysis: An Italian prospective multicentre study. *Nephrol Dial Transplant* 2003; 18 Suppl 7:vii50-4; discussion vii59-62
11. Fry AC, Singh DK, Chandna SM, Farrington K: Relative importance of residual function and convection in determining beta2- microglobulin levels in high-flux haemodialysis and on-line haemodiafiltration. *Blood Purif* 2007; 25: 295-302
12. Twardowski ZJ: Clinical value of standardized equilibration tests in CAPD patients. *Blood Purif* 1989; 7: 95-108
13. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for peritoneal dialysis Adequacy: Update 2000. *Am J Kidney Dis* 2001; 37(suppl 1): S65-S136
14. Yamamoto S, Kasai A, Shimada H: High peritoneal clearance of small molecules did not provide low serum beta2- microglobulin concentrations in peritoneal dialysis patients. *Perit Dial Int* 2003; 23: S34-36
15. Chen HC, Guh JY, Lai YH, Tsai JH: Serial changes of serum beta2-microglobulin in CAPD. *Perit Dial Int* 1993; 13: 238-239
16. Amici G, Virga G, Da Rin G, Grandesso S, Vianello A, Gatti P, Bocci C: Serum beta2-microglobulin level and residual renal function in peritoneal dialysis. *Nephron* 1993; 65: 469-471
17. McCarthy JT, Williams AW, Johnson WJ: Serum beta2-microglobulin concentration in dialysis patients: Importance of intrinsic renal function. *J Lab Clin Med* 1994; 123: 495-505
18. Yoshida H, Yokoyama K, Munakata K, Maruyama Y, Yamamoto R, Hanaoka K, Ikeda M, Yamamoto H, Hosoya T: Superior dialytic clearance of beta2 microglobulin and p-cresol by high-flux hemodialysis as compared to peritoneal dialysis. *Kidney Int* 2007; 71: 467; author reply 467-468
19. Brophy DF, Sowinski KM, Kraus MA, Moe SM, Klaunig JE, Mueller BA: Small and middle molecular weight solute clearance in nocturnal intermittent peritoneal dialysis. *Perit Dial Int* 1999; 19: 534-539
20. Kim DJ, Do JH, Huh W, Kim YG, Oh HY: Dissociation between clearance of small and middle molecules in incremental peritoneal dialysis. *Perit Dial Int* 2001; 21: 462-466
21. Blake P, Burkart JM, Churchill DN, Daugirdas J, Depner T, Hamburger RJ, Hull AR, Korbet SM, Moran J, Nolph KD: Recommended clinical practices for maximizing peritoneal dialysis clearances. *Perit Dial Int* 1996; 16: 448-456
22. Churchill DN, Thorpe KE, Nolph KD, Keshaviah PR, Oreopoulos DG, Pagé D: Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. The Canada-USA (CANUSA) Peritoneal Dialysis Study Group. *J Am Soc Nephrol* 1998; 9: 1285-1292. (Abstract)