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.


BULGULAR: Diyazıt B2M düzeyi ve B2M’nin periton klirensleri yüksek geçirgen grupta düşük geçirgen gruba kıyasla daha yüksekti (sirasiyla 5,92 ± 2,62 mg/L’ye karşın 3,42 ± 1,51mg/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 (sirasiyla 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).


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

**METARIAL 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 dialyse 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 ± 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
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.

**Table I: Demographic and clinical findings of the patients.**

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

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High transporter (n: 25)</th>
<th>Low transporter (n: 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.66 ± 0.64</td>
<td>3.17 ± 0.45</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum B2M (mg/L)</td>
<td>24.1 ± 9.10</td>
<td>27.55 ± 10.10</td>
<td>0.248</td>
</tr>
<tr>
<td>Dialysate B2M (mg/L)</td>
<td>5.92 ± 2.62</td>
<td>3.42 ± 1.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gradient of B2M*</td>
<td>18.23 ± 7.86</td>
<td>23.93 ± 8.98</td>
<td>0.022</td>
</tr>
<tr>
<td>Total Kt/Vurea</td>
<td>2.75 ± 0.83</td>
<td>2.57 ± 0.59</td>
<td>0.376</td>
</tr>
<tr>
<td>Peritoneal clearance of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>creatinine (L/week/1.73m²)</td>
<td>55.58 ± 9.63</td>
<td>50.17 ± 6.48</td>
<td>0.026</td>
</tr>
<tr>
<td>urea (L/week/1.73m²)</td>
<td>64.22 ± 14.03</td>
<td>66.87 ± 8.02</td>
<td>0.420</td>
</tr>
<tr>
<td>B2M (L/week/1.73m²)</td>
<td>11.13 ± 2.14</td>
<td>6.41 ± 1.65</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**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.
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 clearance of 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**


