

# Relationship between peritoneal permeability with inflammation and subclinical atherosclerosis in peritoneal dialysis patients

Ozlem Yayar<sup>1</sup>, Baris Eser<sup>2</sup>, Alper Bozkurt<sup>3</sup>

<sup>1</sup>Canakkale State Hospital, Department of Nephrology, Canakkale, Turkey

<sup>2</sup>Hitit University, Erol Olcok Training and Research Hospital, Department of Nephrology, Corum, Turkey

<sup>3</sup>Private 100th Year Hospital, Department of Radiology, Ankara, Turkey

## Abstract

**Aim:** High permeability in peritoneal dialysis (PD) is reported to be associated with increased mortality. Cardiovascular disease is the most important cause of morbidity and mortality in patients with end-stage renal disease. The inflammation is thought to take part in development of atherosclerosis. The aim of this study is to investigate the relation of peritoneal permeability type with carotid intima media thickness (CIMT) in PD patients.

**Material and Methods:** Based on the standard peritoneal equilibration test, 56 PD patients (28 male) were divided in two transporter groups: low (low+low average) and high (high+high average) permeability. C-reactive protein (CRP) measured as a marker of inflammation and CIMT was evaluated by high-resolution B-mode ultrasonography.

**Results:** Twenty one patients were low and 35 of them were high peritoneal transporters. Mean CRP level was significantly higher in the high permeability group (HPG) ( $1.62 \pm 1.7$  vs  $0.84 \pm 1$  mg/dL;  $p=0.006$ ). CIMT was higher in the HPG but this difference did not reach statistical significance ( $0.810 \pm 0.160$  vs  $0.740 \pm 0.160$  mm;  $p=0.16$ ).

**Conclusions:** CRP, an indicator of inflammation, was found to be higher in the HPG. CIMT also was found to be higher in HPG although it was not statistically significant. One of the causes of increased mortality rate in this group of patients may be explained by inflammation and atherosclerosis.

**Keywords:** Atherosclerosis; Inflammation; Peritoneal Dialysis; Peritoneal Permeability.

## INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of mortality in end-stage renal disease (ESRD) patients, accounting nearly 40% of all-cause mortality (1). Non-traditional risk factors, as well as traditional risk factors such as diabetes, hypertension, smoking, and dyslipidemia, contribute to a high prevalence of CVD and mortality in dialysis patients (2). Chronic inflammation as a non-traditional risk factor is shown to be an important predictor of morbidity and mortality in ESRD patients (3). The causes of chronic inflammation in dialysis patients are multifactorial (4).

Uremia per se (5) decreased residual renal function (RRF) (6,7), periodontal disease (8), and infection of microorganisms such as Chlamydia pneumonia (9) induce the production of pro-inflammatory cytokines such as

CRP and interleukin-6 (IL-6). Specifically, in peritoneal dialysis (PD) patients, dialysis catheter implantation, bio-incompatibility of PD solutions, and exposure of endotoxins can induce inflammatory reactions in the peritoneum and might cause increased inflammatory status in PD patients (4,10).

Peritoneal membrane function assessed by the peritoneal equilibration test is associated with clinical outcomes in PD patients and showed high transport status to be associated with poor survival in these patients (11).

As a sign of atherosclerosis increased carotid intima-media thickness (CIMT) is widely used and accepted as a strong predictor of cardiovascular events and mortality in ESRD patients (12). The aim of this study is to determine the relationship of inflammation and subclinical atherosclerosis in high-peritoneal transporters.

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**Corresponding Author:** Baris Eser, Hitit University, Erol Olcok Training and Research Hospital, Department of Nephrology, Corum, Turkey, E-mail: beser374@gmail.com

## MATERIAL and METHODS

### Study Population

This cross-sectional study included 56 PD patients and was approved by the local ethics committee and was conducted in accordance with Declaration of Helsinki. All participants provided written informed consent to participate in the study.

All subjects were clinically stable at the time of evaluation. Exclusion criteria were the presence of infection (acute and chronic), known collagen vascular disease, malignancy history and recent history of a cardiovascular disease diagnosed by angiography or scintigraphy. Patients who had PD catheter insertion in last 30 days were also excluded. Peritoneal dialysis patients followed by nephrology outpatient department were included in the study. For all patients, demographic parameters and comorbidities at the time of inclusion were recorded from patients' medical files.

### Laboratory

To simulate the actual dialysis conditions, all patients had a full abdomen at the time of sampling. Blood samples for laboratory measurements were drawn from the antecubital vein 2 hours after the first PD exchange after overnight fasting. Serum was separated from blood within 30 minutes.

Serum total cholesterol and triglyceride levels were measured by colorimetric analysis (GPO-PAP and CHOD-PAP; Boehringer-Mannheim, Mannheim, Germany). High-density lipoprotein cholesterol was measured by phosphotungstic acid precipitation method. CRP was measured by the immunonephelometric method (IMECE). Other biochemical parameters were measured by computerized auto analyzer (Hitachi 717; Boehringer-Mannheim).

### Peritoneal Equilibration Test (PET) and Assessment of Dialysis Adequacy

A modified PET using 4.25% glucose dialysate was performed and the value of the dialysate-to-plasma creatinine ratio at 4 h was calculated as previously reported (18).

The patients were grouped as high (high+high average) and low (low+low average) transporters according to modified PET test. In addition, urea kinetic studies were performed from a 24-hour collection of dialysate and urine at baseline. Kt/V urea was determined from the total loss of urea nitrogen in spent dialysate using PD Adequest 2.0 for Windows software (Baxter Healthcare, Deerfield, Ill., USA). Residual glomerular filtration rate (GFR) was estimated by a 24-hour urine collection.

### Measurement of Carotid Intima-Media Thickness

Ultrasonographical B-mode imaging of bilateral carotid arteries was performed with a high-resolution real-time ultrasonography with a 12MHz linear-assay transducer (Mindray DC7, China). Evaluations were performed by a single trained radiologist who was blinded to the clinical status and laboratory parameters of the patients. Common

carotid arteries, carotid bulb and internal carotid arteries were examined by two different longitudinal projections. At each longitudinal projection, CIMT was conducted from the site of the greater thickness. CIMT was defined as the distance between the leading edges of the lumen interface at the far wall in plaque-free arterial segments. Three different measurements were taken. The value was expressed as an average of the maximal CIMT.

### Statistical analysis

Statistical analysis was performed by using statistical package SPSS version 19.0 (SPSS Inc., IL, USA). All variables were expressed as the mean  $\pm$  SD unless otherwise indicated. The Kolmogorov-Smirnov test was used to analyze the normality of distribution. Pearson's correlation analysis was used to evaluate the relation between CIMT, CRP and other parameters. Patients were grouped in two according to the transport status. Parameters shown to correlate with CIMT were analyzed by linear regression analysis. A level of  $p < 0.05$  was accepted as significant.

## RESULTS

Baseline characteristics of the patients are shown in Table 1.

**Table 1. Properties of patients**

| Variable                 | n=56              |
|--------------------------|-------------------|
| Age, years               | 46.3 $\pm$ 13.2   |
| Gender, female; n, (%)   | 28 (50)           |
| DV, months               | 67.7 $\pm$ 38.6   |
| Past peritonitis, n, (%) | 20 (35.7)         |
| Diabetes, n, %           | 7 (12.5)          |
| Hypertension, n, (%)     | 34 (60.7)         |
| Smoking, n, (%)          | 13 (23.2)         |
| MAP, mmHg                | 98.3 $\pm$ 18.7   |
| BMI, kg/m <sup>2</sup>   | 25.2 $\pm$ 3.8    |
| Kt/V                     | 2.1 $\pm$ 0.43    |
| Glucose, mg/dL           | 104 $\pm$ 23      |
| Albumin, g/dL            | 3.78 $\pm$ 0.4    |
| Hemoglobin, g/dL         | 11.4 $\pm$ 1.9    |
| Ferritin, ng/mL          | 293 $\pm$ 388     |
| CRP, g/dL                | 1.33 $\pm$ 1.5    |
| Calcium, mg/dL           | 9.2 $\pm$ 0.7     |
| Phosphorus, mg/dL        | 4.9 $\pm$ 1.4     |
| Parathormone, pg/mL      | 484 $\pm$ 326     |
| T.chol, mg/dL            | 186 $\pm$ 45      |
| LDL-chol, mg/dL          | 111 $\pm$ 34      |
| Triglyceride, mg/dL      | 175 $\pm$ 110     |
| CIMT, mm                 | 0.790 $\pm$ 0.160 |

**BMI: Body mass index, CRP: C-reactive protein, CIMT; carotid intima-media thickness, DV; Dialysis vintage, LDL-chol; low density lipoprotein cholesterol, MAP: Mean arterial pressure, T.Chol; Total cholesterol**

Mean age was 46.3 ± 13.2 years, mean duration of dialysis was 67.7 ± 38.6 months and 50% of the patients were female. The prevalence of diabetes and hypertension was 12.5% and 60.7% respectively.

Based on the modified PET, 56 PD patients were grouped in two: Low (low+low average, n=21) and high (high+high average, n=35) permeability. Comparison of groups can be seen in Table 2.

**Table 2. Comparison of low and high peritoneal transport group**

| Variable                 | Low transport (n=21) | High transport (n=35) | p     |
|--------------------------|----------------------|-----------------------|-------|
| Age, years               | 42.6 ± 12.1          | 48.6 ± 13.4           | 0.12  |
| Gender, female; n, (%)   | 11 (52.4)            | 17 (48)               | 0.78  |
| DV, months               | 68.2 ± 34.0          | 70.9 ± 25.6           | 0.45  |
| Past peritonitis, n, (%) | 6 (28.6)             | 14 (40)               | 0.39  |
| Diabetes, n (%)          | 2 (9.5)              | 5 (14.3)              | 0.6   |
| Hypertension, n, (%)     | 11 (52.4)            | 23 (65.7)             | 0.32  |
| Smoking, n, (%)          | 3 (14.3)             | 10 (28.6)             | 0.22  |
| MAP, mmHg                | 97.9 ± 19.2          | 98.6 ± 18.7           | 0.63  |
| BMI, kg/m <sup>2</sup>   | 24.1 ± 3.5           | 25.8 ± 3.8            | 0.11  |
| Kt/V                     | 2.2 ± 0.4            | 2.0 ± 0.5             | 0.13  |
| Glucose, mg/dL           | 105 ± 31.1           | 103 ± 16              | 0.25  |
| Albumin, g/dL            | 3.9 ± 0.4            | 3.7 ± 0.4             | 0.33  |
| Hemoglobin, g/dL         | 11.4 ± 1.8           | 11.3 ± 2.0            | 0.78  |
| Ferritin, ng/mL          | 303 ± 453            | 287 ± 350             | 0.33  |
| CRP, g/dL                | 0.8 ± 1.0            | 1.62 ± 1.7            | 0.006 |
| Calcium, mg/dL           | 9.1 ± 0.6            | 9.2 ± 0.8             | 0.67  |
| Phosphorus, mg/dL        | 5.1 ± 1.5            | 4.9 ± 1.3             | 0.65  |
| Parathormone, pg/mL      | 531 ± 334            | 456 ± 324             | 0.38  |
| T.chol, mg/dL            | 182 ± 50             | 188 ± 43              | 0.56  |
| LDL-chol, mg/dL          | 108 ± 36             | 111.9 ± 33.4          | 0.77  |
| Triglyceride, mg/dL      | 145 ± 95             | 193 ± 116             | 0.25  |
| CIMT, mm                 | 0.740 ± 0.160        | 0.810 ± 0.160         | 0.16  |

**BMI: Body mass index, CRP: C-reactive protein, CIMT; carotid intima-media thickness, DV; Dialysis vintage, LDL-chol; low density lipoprotein cholesterol, MAP: Mean arterial pressure, T.Chol; Total cholesterol**

There were no difference in terms of age (42.6 ± 12.1 vs 48.6 ± 13.4; p = 0.12) and albumin (3.9±0.4 vs 3.7 ± 0.4; p = 0.33) levels. CRP was found to be statistically significantly higher in the high transport group (0.8 ± 1.0 vs 1.62 ± 1.7; p = 0.006). CIMT tends to be higher in high transport group but this was not statistically significant (0.740 ± 0.160 vs 0.810 ± 0.160; p = 0.16).

Patients were grouped in two according to types of PD solutions (conventional and biocompatible solutions, Table 3). Thirty-one of the patients were using conventional PD solutions while 25 of them were using biocompatible PD solutions. The only difference between two groups was the PD vintage (84.2 ± 35.1 months in the conventional

group and 47.3 ± 33 months in biocompatible solution group p < 0.05). CRP and transport rate was not different between groups.

Patients were grouped in two according to the presence of renal residual function (RRF) (Table 4). Nineteen (33.9%) of the patients had RRF and the only statistically significant difference between two groups was dialysis vintage (83 ± 33.3 in RRF (-) vs 38.1 ± 30.4 in RRF (+); p < 0.001).

Correlation analysis of CRP and CIMT was made in high transport group. In the high transport group CRP was found to be positively correlated with dialysis vintage (r = 0.268; p = 0.046), CIMT (r = 0.284; p = 0.034) and negatively correlated with ultrafiltration volume (r = -0.300; p = 0.025). In the high transport group CIMT was found to be positively correlated with age (r=0.49; p < 0.001) and CRP (r = 0.284; p = 0.034), (Figure 1). In low transport group CRP was correlated with dialysis vintage (r = 0.272; p = 0.047). In low transport group CIMT was positively correlated with age (r = 0.42; p = 0.01).

In a linear regression analysis in the high transport group, the model including CRP and age were found to be statistically significant (F = 11.39; p < 0.001). When the parameters are analyzed age factor (β = 0.471; P < 0.001) and CRP (β = 0.247; p = 0.037) were found to be independent determinants of CIMT. R<sup>2</sup> value explaining the overall biological variability in CIMT explained by age and CRP was found to be 0.301.

**Table 3. Comparison of patients according to peritoneal dialysis solutions**

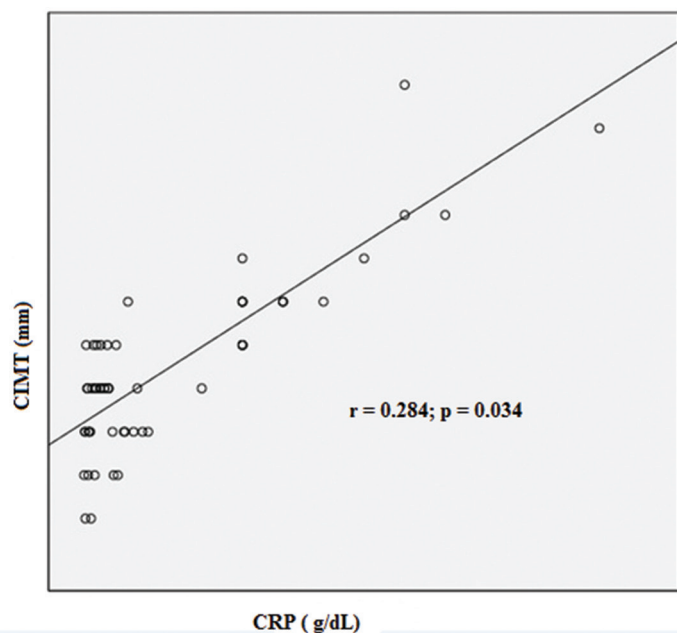
| Variable                 | Conventional (n=31) | Biocompatible (n=25) | P       |
|--------------------------|---------------------|----------------------|---------|
| Age, years               | 47 ± 13.6           | 45.5 ± 12.8          | 0.627   |
| Gender, female; n, (%)   | 14 (45.2)           | 14 (56)              | 0.42    |
| DV, months               | 84.2 ± 35.1         | 47.3 ± 33.0          | < 0.001 |
| Past peritonitis, n, (%) | 9 (29)              | 11 (44)              | 0.245   |
| Diabetes, n, (%)         | 4 (12.9)            | 3 (12)               | 0.919   |
| Hypertension, n, (%)     | 19 (61.3)           | 15 (60)              | 0.922   |
| Smoking, n, (%)          | 6 (19.4)            | 7 (28)               | 0.446   |
| HPTR, n, (%)             | 21 (67)             | 14 (56)              | 0.367   |
| MAP, mmHg                | 95.2 ± 12.3         | 102.1 ± 24.2         | 0.206   |
| BMI, kg/m <sup>2</sup>   | 24.3 ± 3.9          | 26.2 ± 3.4           | 0.075   |
| Kt/V                     | 2.1 ± 0.4           | 2.1 ± 0.5            | 0.830   |
| Glucose, mg/dL           | 105 ± 22            | 102 ± 24             | 0.225   |
| Albumin, g/dL            | 3.8 ± 0.4           | 3.8 ± 0.4            | 0.656   |
| Hemoglobin, g/dL         | 11.6 ± 2.0          | 11 ± 1.8             | 0.410   |
| C-reactive protein, g/dL | 1.3 ± 1.2           | 1.4 ± 1.9            | 0.662   |
| Calcium, mg/dL           | 9.3 ± 0.7           | 9.1 ± 0.7            | 0.400   |
| Phosphorus, mg/dL        | 4.8 ± 1.4           | 5.2 ± 1.2            | 0.287   |
| Parathormone, pg/mL      | 485 ± 353           | 484 ± 297            | 0.742   |
| LDL-chol, mg/dL          | 110 ± 39            | 111 ± 28             | 0.792   |
| Triglyceride, mg/dL      | 196 ± 124           | 148 ± 84             | 0.174   |
| CIMT, mm                 | 0.770 ± 0.160       | 0.810 ± 0.170        | 0.666   |

**BMI: Body mass index, CIMT; Carotid intima-media thickness, DV; Dialysis vintage, HPTR: High Peritoneal Transport Rate, LDL-chol; low density lipoprotein cholesterol, MAP: Mean arterial pressure**

**Table 4. Comparison of patients according to renal residual function (RRF)**

| Variable                 | RRF (-) (n=37) | RRF (+) (n=19) | p       |
|--------------------------|----------------|----------------|---------|
| Age, years               | 44.9 ± 12.4    | 49.2 ± 14.5    | 0.24    |
| Gender, female; n, (%)   | 20 (54.1)      | 8 (42.1)       | 0.40    |
| DV, months               | 83 ± 33.3      | 38.1 ± 30.4    | < 0.001 |
| Past peritonitis, n, (%) | 11 (29.7)      | 9 (47.9)       | 0.19    |
| Diabetes, n, (%)         | 3 (8.1)        | 4 (21.1)       | 0.17    |
| Hypertension, n, (%)     | 21 (56.8)      | 13 (68.4)      | 0.40    |
| HPTR, n, (%)             | 23 (62.2)      | 12 (63.2)      | 0.94    |
| MAP, mmHg                | 95.8 ± 18.5    | 103.2 ± 18.6   | 0.08    |
| BMI, kg/m <sup>2</sup>   | 25.0 ± 3.7     | 25.5 ± 4.0     | 0.79    |
| Kt/V                     | 2.1 ± 0.4      | 2.06 ± 0.5     | 0.56    |
| Glucose, mg/dL           | 101 ± 21       | 108 ± 26       | 0.29    |
| Albumin, g/dL            | 3.8 ± 0.4      | 3.7 ± 0.4      | 0.09    |
| Hemoglobin, g/dL         | 11.4 ± 2.2     | 11.3 ± 1.4     | 0.99    |
| CRP, g/dL                | 1.22 ± 1.1     | 1.6 ± 2.1      | 0.93    |
| Calcium, mg/dL           | 9.3 ± 0.7      | 9.0 ± 0.6      | 0.14    |
| Phosphorus, mg/dL        | 5.0 ± 1.4      | 4.9 ± 1.3      | 0.76    |
| Parathormone, pg/mL      | 531 ± 351      | 394 ± 258      | 0.18    |
| LDL-cholesterol, mg/dL   | 111 ± 35       | 110 ± 33.1     | 0.99    |
| Triglyceride, mg/dL      | 199 ± 124      | 128 ± 53       | 0.07    |
| CIMT, mm                 | 0.780 ± 0.140  | 0.790 ± 0.210  | 0.87    |

**BMI: Body mass index, CRP: C-reactive protein, CIMT; Carotid intima-media thickness, DV; Dialysis vintage, HPTR: High Peritoneal Transport Rate, LDL-cholesterol; Low density lipoprotein cholesterol, MAP: Mean arterial pressure**



**Figure 1.** Distribution graph of relationship between carotid intima-media thickness and c-reactive protein

## DISCUSSION

There are two main findings of this study: first CRP level is found to be higher in high transporters in respect to low transporters, second CRP and age are found to be independent determinants of CIMT in high transport group.

Chronic inflammation is implicated in increased cardiovascular risk, and CVD is the most common cause of death in ESRD patients (13, 14). CRP has emerged as a useful biomarker for vascular inflammation associated with atherosclerosis. Determination of CRP levels is currently recommended by the American Heart Association in all patients at a risk of CVD (15). Also, the decrease in RRF is connected to a stronger inflammatory response in peritoneal dialysis patients with higher concentrations of CRP (16-18). In our study, CRP was not different between the patients having RRF or not.

Increased CIMT, one of the first signs of early atherosclerosis, is related to high blood pressure, dyslipidemia, hyper-homocysteinemia and micro-inflammation (19, 20). Elevated serum concentrations of CRP is another marker used to stratify CV risk by reflecting chronic inflammation in adult and pediatric CKD and dialysis patients (9, 21-23). Both CIMT and CRP are found to be elevated in pediatric and adult dialysis patients in recent studies (24-27). In our study, although CIMT was not different between groups, correlation analysis yielded CRP and age to be independent determinants of CIMT in high transport group.

Peritoneal membrane function assessed by the peritoneal equilibration test is associated with clinical outcomes in PD patients (11). Previous reports showed high transport status to be associated with poor survival in PD patients (11, 28). Moreover, malnutrition and chronic inflammation are prevalent in high transporters (29-32). Low serum albumin level correlates with malnutrition (28) and is strongly predictive of PD patient mortality (29, 30). The greater prevalence of hypo-albuminemia in high transporters may also arise from hemo-dilution secondary to suboptimal ultrafiltration (31) or from excessive peritoneal protein losses (32). Alternatively, hypoalbuminemia in high transporters may reflect a greater incidence of underlying chronic inflammation (7, 33), although other studies have not observed a significant correlation between dialysate/plasma creatinine 4 h and various inflammatory markers, such as CRP (34). In this study, CRP was found to be positively correlated with dialysis vintage in high transporters. Uremia, peritoneal glucose exposure, and peritonitis can cause local inflammation, in turn, increasing systemic inflammation. As the time on dialysis increases, augmentation of inflammation may be suspected.

Conventional PD solutions are accused of the change in membrane function and inflammation. The potential mechanisms whereby conventional dialysate might drive membrane injury are many and include non-physiological pH (acidic, typically 5.2), lactate buffer,

increased osmolality, high glucose concentrations, and high glucose degradation product (GDP) concentrations. The evidence that low GDP solutions are associated with preservation of mesothelium cells is reasonably compelling from biomarker studies, in particular the increase in dialysate CA-125 levels associated with the use of all the tested biocompatible solutions so far (35) and in one case evidence for reduced epithelial to mesenchymal transition in their morphologic appearance (36). However in our study when patients are compared in terms of biocompatibility of solutions high transporter number was high in conventional solution group but this difference was not statistically different.

In our study, CRP levels were not different between two PD solution groups. Pajek et al. (37) compared the short-term effects of a low GDP peritoneal dialysis solution and a conventional PDS in the intraperitoneal and systemic inflammation. According to the authors, despite the significant reduction of intraperitoneal IL-6 concentration in patients using the bicarbonate and lactate solution, the serum levels of inflammatory markers did not differ between the two solutions. Additionally, the authors did not observe significant difference in the degree of systemic inflammation between both treatments. However, one has to consider that the absence of inflammation signs in both groups in our study may be caused by the nature of the study. This was a cross-sectional study and some of the patients using biocompatible solutions now used conventional solutions before.

There are some limitations of this study. Firstly, this is a cross-sectional study focusing on the relation of peritoneal transport rate with atherosclerosis detected by CIMT. Secondly, the sample size is relatively small. Thirdly, this is not a prospective controlled study so we cannot draw cause-and-effect relationship from our findings. Finally, CIMT measurement is a relatively subjective measurement; computerized programs are used to reduce the error incidence, but we could not use it. Also, we could not use hs-CRP because of financial issues.

In conclusion, inflammation and sub-clinical atherosclerosis is increased in high peritoneal transport group. Mortality increased in this group may be associated with increased inflammation and atherosclerosis.

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