The Association Between Progression of Carotid Artery Intima-Media Thickness and Cardiovascular Events in Peritoneal Dialysis Patients

Periton Diyalizi Hastalarında Karotis Arter İntima Media Kalınlığı Progresyonu ile Kardiyovasküler Olaylar Arasındaki İlişki

ABSTRACT

OBJECTIVE: Measurement of carotid artery intima-media thickness (CA-IMT) is directly associated with cardiovascular (CV) outcomes. We retrospectively investigated the impact of CA-IMT progression on new CV events in patients on peritoneal dialysis (PD).

MATERIAL and METHODS: All PD patients who have been followed in our unit (n=163) were screened. The patients who had no CA-IMT were excluded. Ninety-six patients who had baseline CA-IMT measurement were included. Fifty-two patients had second CA-IMT measurement. Fatal and nonfatal CV events were screened from patients' charts.

RESULTS: At baseline, mean CA-IMT was 0.62±0.16 mm (median 0.60 mm). In patients treated with PD more than 2 years, CV event rate was higher in patients with high CA-IMT (>0.60 mm) compared to the patients with low CA-IMT at baseline (22.2% versus 4.2%, p=0.041).

In patients who had second CA-IMT measurement, mean CA-IMT increased from 0.62±0.17 mm to 0.66±0.17 mm (p=0.002). In ROC analysis, best cut-off value of CA-IMT progression was 0.0062 mm/month for prediction of CV events (AUC 0.752±0.066, p=0.046). When patients were grouped according to this cut-off value, CV event rate was higher in patients showed CA-IMT progression above 0.0062 mm/month (33.3% versus 2.7%, p=0.001). In Cox-regression analysis, progression of CA-IMT more than 0.0062 mm/month was only predictor for new CV events (ExpB=14.57, p=0.015).

CONCLUSION: Consecutive assessment of atherosclerosis progression by CA-IMT measurement has importance for prediction of new CV events in PD patients.

KEY WORDS: Progression of atherosclerosis, Carotid artery intima-media thickness, Cardiovascular events, Peritoneal dialysis

ÖZ

AMAÇ: Karotis arter intima media kalınlığı (KA-İMK) ölçümü aterosklerotik kardiyovasküler sonlanımlar ile ilişkilidir. Retrospektif olan bu çalışmada, periton diyalizi yapan hastalarda KA-İMK progresyonunun yeni gelişen kardiyovasküler (KV) olaylar üzerine etkisini araştırdık.

GEREÇ ve YÖNTEMLER: Periton diyalizi ünitemizde takip edilen hastaların (n=163) dosyaları tarandı. KA-İMK ölçümü olmayan hastalar dışlandı. Bazal KA-İMK ölçümü olan 96 hasta çalışmaya dahil edildi. İkinci KA-İMK ölçümü olan 52 hasta mevcuttu. Ölümcül ve ölümcül olmayan KV olaylar hasta dosyalarından tarandı.

BULGULAR: Bazalde ortalama KA-İMK 0.62±0.16 mm (medyan 0.60 mm) idi. İki yıldan fazla süreyle PD yapan hastalarda, bazal KA-İMK 0.60 mm'nin üzerinde olanlarda olmayanlara göre KV olay oranı daha yüksekti (%22.2'ye karşılık %4.2, p=0.041).

İkinci kez KA-İMK ölçülen hastalarda ortalama KA-İMK 0.62±0.17 mm'den 0.66±0.17 mm'ye yükseldi (p=0.002). ROC eğrisinde KV olay için saptanan en iyi cut-off değeri 0.0062 mm/ay idi. (AUC 0.752±0.066, p=0.046). Hastalar bu değerine göre iki gruba ayrıldığında aylık progresyonu 0.0062 mm'nin üzerinde olanlarda olmayanlara göre KV olay daha yüksek saptandı (%33.3'e karşılık

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%2.7, p=0.001). Cox regresyon analizinde geleneksel risk faktörleri de değerlendirmeye alındığında, KV olay belirleyicisi sadece aylık KA-İMK progresyonunun 0.0062 mm olması idi (ExpB=14.57, p=0.015).

SONUÇ: Periton diyalizi hastalarında KA-İMK ölçümü ile aterosklerozun progresyonunun takibi, yeni gelişebilecek KV olayların belirlenmesinde önemlidir.

ANAHTAR SÖZCÜKLER: Ateroskleroz progresyonu, Karotis arter intima media kalınlığı, Kardiyovasküler olaylar, Periton diyalizi

INTRODUCTION

Cardiovascular (CV) disease is the major cause of mortality in dialysis patients. The CV mortality rate, even adjusted with traditional risk factors such as age, gender and diabetes, is 30-fold higher in dialysis patients compared to the general population (1-3). Accelerated atherosclerosis is the main pathophysiological mechanism associated with the development and progression of CV disease in patients with end-stage renal disease (4, 5).

Measurement of carotid artery intima-media thickness (CA-IMT) is a reliable method for assessment of subclinical atherosclerosis. In the nonuremic population, CA-IMT has been associated with CV outcomes (6, 7). In patients with end-stage renal disease, who have higher CV risk profile, there is no sufficient data about the relationship between the progression of CA-IMT and the development of new CV events.

In this study, we retrospectively investigated the impact of CA-IMT progression on new CV events in patients treated with chronic peritoneal dialysis (PD).

MATERIAL and METHODS

Between April 2007 and April 2011, all PD patients who have been followed in our unit (n=163) were screened. The patients who had no CA-IMT were excluded. Ninety-six patients who had baseline CA-IMT measurement were included. A total of 52 patients had second CA-IMT measurement after a mean of 16 months (6-33 months). Fatal and nonfatal CV events (CV death, acute myocardial infarction, unstable angina pectoris requiring hospitalization, peripheral vascular disease, new onset or worsening congestive heart failure and stroke) were screened from patients' charts.

CA-IMT Measurement

Common CA-IMT was assessed by using high-resolution colour Doppler ultrasound unit (HDI 5000, Philips, Bothell, WA, USA) equipped with 5–12-MHz broadband electronic linear array transducer. All procedures were performed on both sides of two longitudinal images of the each common carotid artery on the morning by the same operator. Average of two CA-IMT values from each side were used to calculate mean CA-IMT. The most distal 1-cm segment (just proximal to the bulbar dilatation) of both common carotid arteries were scanned on longitudinal plane to achieve IMT values. The echogenic inner line (representing the lumen-intima interface) and adjacent hypoechoic layer (media) of the far wall of the artery were measured together to get the CA-IMT value. Values from both sides were averaged to obtain the mean CA-IMT of each donor. Intra-observer coefficient of variation was 2.9%.

Follow-up Data

The following variables were obtained from patient charts: age, gender, body weight and height, history of diabetes and CV disease, use of antihypertensive and statin, duration of PD, PD modality, blood pressure and pulse pressure, residual urine output, presence of anuria (diuresis ≤100 mL/day), ultrafiltration, serum creatinine, albumin, C-reactive protein (CRP), calcium, phosphorus, parathyroid hormone, glucose, HbA1c, total cholesterol, low density lipoprotein, triglycerides, peritoneal equilibration test (PET), weekly total Kt/V urea and weekly total creatinine clearance (CCr). Peritoneal transport status was analysed as a categorical variable according to the four groupings of D–P Cr 4-h values defined by Twardowski *et al*. (low, ≤0.50; low average, 0.50–0.64; high average, 0.65–0.80; and high, ≥0.81) (8). The follow-up parameters of patients were calculated as the time-averaged.

Statistical Analyses

Continuous variables with normal distribution were expressed as means ± standard deviation, while those without normal distribution were shown as median. Comparisons between the two groups were done by student's t test or χ2 test. Univariate analysis was done to explore relationships between CA-IMT and other variables by Pearson correlation test for normally distributed data and Spearman Rank correlation test for non-parametric data. Step-wise multiple linear regression analysis was used to assess the independent determinants of increased CA-IMT. Cardiovascular event rate was determined using the Kaplan-Meier method and compared using the log-rank test. We sought the best cut-off threshold value of CA-IMT progression for new CV event rate using the ROC curve. The relationship between usual cardiovascular markers and new CV events was analyzed by univariate and multivariate Cox regression. A two tailed P < 0.05 was considered as statistically significant. All statistical analyses were performed using the SPSS statistical software 15.0 for Windows (SPSS, Chicago Davis, IL. USA).
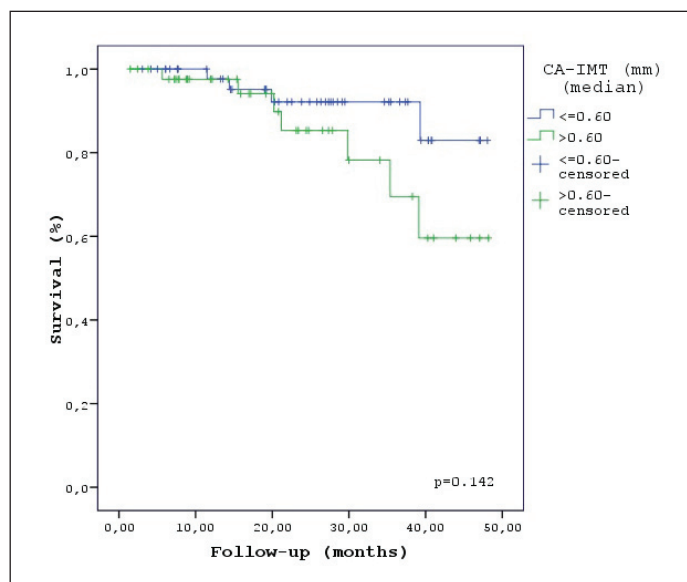
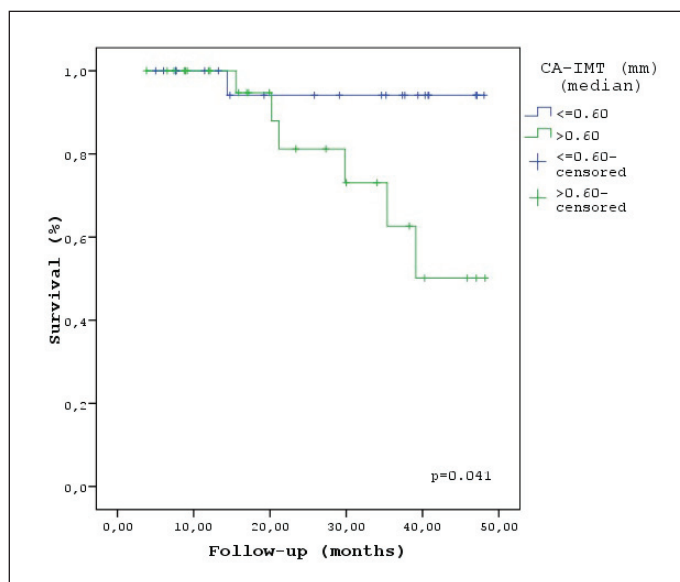*Figure 1: Kaplan-Meier Curve for fatal and nonfatal CV events based on median CA-IMT in all patients.*

Figure 2: Kaplan-Meier Curve for fatal and nonfatal CV events based on median CA-IMT in a subgroup of the patients who were on PD treatment more than two years (n=51).
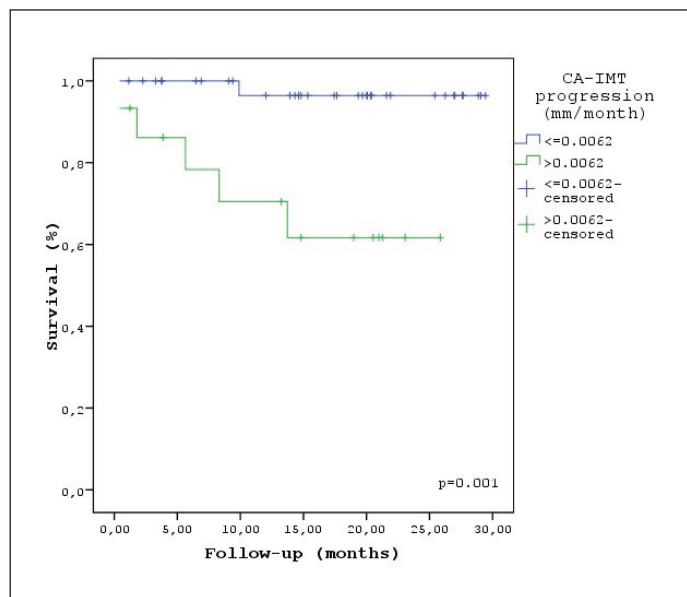

Figure 3: Kaplan-Meier Curve for fatal and nonfatal CV events based on 0.0062 mm/month progression of CA-IMT.

RESULTS

Baseline Characteristics

Mean age was 49± 14 years in the patients who had baseline CA-IMT measurement (n=96). The prevalence of diabetes and CV disease history were 10.4% and 7.2%, respectively. Mean CA-IMT was 0.62± 0.16 mm (median: 0.60 mm). Baseline parameters were shown in Table I. The proportion of the patients with high or high- average PET results was 17.2%.

Baseline CA-IMT was positively correlated with age (r=0.698,), body surface area(r=0.471, p<0.001), HbA1c level (r=0.380, p=0.01) and LDL cholesterol (r=0.196, p=0.05). CA-IMT was higher in males (p<0.001) and in patients with diabetes (p=0.001) or CV disease P=0.028). In step-wise multiple linear regression analysis age (t=6.93, p<0.001), male gender (t=2.85, p=0.006) and presence of diabetes (t=2.11, p=0.38) were predictors for CA-IMT when adjusted with time on PD duration, history of CV disease, body surface area, mean arterial blood pressure, LDL cholesterol and HbA1c level.

Follow-up Data

During 23 months of follow-up, new CV event rate was 11.5% (9 CV deaths (n=9) and stroke (n=2)) in the studied population. There was no association between baseline CA-IMT and new CV events. When patients were grouped according to the value of median CA-IMT, CV event rate was more likely to be in higher group, but there was no significant difference. (Figure 1). In a subgroup of the patients who were on PD treatment more than two years (n=51), CV event rate was higher in patients with CA-IMT >0.60 mm compared to the patients with CA-IMT <0.60 mm (22.2% versus 4.2%, p=0.04, respectively (Figure 2).

In the patients with two CA-IMT measurements (n=52), CA-IMT progressed from 0.62±0.17 mm to 0.66±0.17 mm during the follow-up (p=0.002). Progression rate of CA-IMT was established 0.033±0.086 mm/year. The percent of patients changed CA-IMT positively was 57.6% (n=30). After the second measurement of CA-IMT, new CV event rate was 11.5% in this

Table I: Baseline characteristics of the patients who had baseline CA-IMT measurement.

Patients (n)	96
Age (years)	49 ± 14
Male (%)	42
Time on PD (months, median)	29
Automatized PD (%)	19.8
Diabetes (%)	10.4
History of CVD (%)	7.2
Anti-hypertensive medication (%)	13.5
Anti-lipidemic medication (%)	23
Anuria (%)	27.4
Body surface area (m^2)	1.74 ± 0.20
Mean arterial blood pressure (mmHg)	94 ± 18
Pulse pressure (mmHg)	41 ± 14
Total Kt/V urea	2.49 ± 0.65
Total CCr (L/1.73 m^2/week)	79 ± 49
Glucose (mg/dl)	102 ± 31
HbA1c (%)	5.24 ± 0.69
CRP (mg/dl)	0.94 ± 1.15
Total cholesterol (mg/dl)	211 ± 47
Triglyceride (mg/dl)	176 ± 73
LDL cholesterol (mg/dl)	127 ± 39
Albumin (g/dl)	3.96 ± 0.48
CA-IMT (mm)(median)	0.62 ±0.16 (0.60)
CA-IMT plaque (n=20)	1.56 ± 0.59

PD: Peritoneal Dialysis, **CVD:** Cardiovascular Disease, **CCr:** Creatinine Clearance, **CRP:** C-Reactive Protein, **LDL:** Low Density Lipoprotein, **CA-IMT:** Carotid Artery Intima-Media Thickness

population during the mean 16 (0.4-29) months of follow-up (CV death (n=5), stroke (n=1)).

The best cut-off value of CA-IMT progression for prediction of new CV events was 0.0062 mm/month (AUC=0.752, p=0.04). New CV event rate was 33.3% in the patients with CA-IMT progression above 0.0062 (progressors) compared to others (nonprogressors) (%2.7), p=0.001 (Figure 3).

The progressors were more likely to be male, anuric, had longer time on PD, higher blood pressure, pulse pressure, CRP, phosphorus, calcium-phosphate product and PTH, and lower total Kt/V urea, total weekly CCr, residual urine volume and baseline CA-IMT compared to the nonprogressors, but the difference was not significant (Table II). In adjusted Cox-regression analysis, monthly progression rate of CA-IMT (0.006 mm) was found as predictor for new CV events (RR: 14.57, p=0.01) with sensitivity of 83%, specificity of 79%, positive predictive value of 33%, negative predictive value of 97.

DISCUSSION

We report the first time that CA-IMT progression predicts new CV events in patients treated with peritoneal dialysis.

In nonuremic subjects, measurement of CA-IMT is apparently the most commonly used marker for atherosclerosis and is directly associated with atherosclerotic CV outcomes. Recently, it has been reported that CA-IMT progression meets the criteria of a surrogate for CV disease endpoints and may be considered as a valid alternative for CV events as outcome (7).

In treated hypertensive patients, baseline CA-IMT, but not progression rate of CA-IMT, was shown to be associated with CV outcomes independently of blood pressure and traditional risk factors (9). In a recent meta-analysis (10) of CA-IMT progression to predict cardiovascular events in the general population, while baseline and final CA-IMT was significantly associated with cardiovascular risk, it was not detected any associations with progression of CA-IMT, as similar to the previous study. CV disease prevalence is extremely high in the presence of end-stage renal disease. CA-IMT was higher in patients treated with PD compared to the general population (11,12). Furthermore, in addition to traditional risk factors, nontraditional risk factors unique for uremia such as ADMA, oxidative stress, several adhesion molecules and inflammatory markers seem to be responsible for the development of atherosclerosis in PD patients (12-14). To investigate the impact of CA-IMT progression on new CV events in PD patients is rational because of the presence of accelerated atherosclerosis in this population (4, 5).

In prevalent hemodialysis patients, per 0.1 mm increase in CA-IMT was associated with 41% increased risk for CV mortality during the 5 years of follow-up period (15). In patients with end-stage renal disease including 47 PD patients, CA-IMT has been associated with left ventricular mass index and per 0.1 mm increase in CA-IMT was associated with 24% increased risk for CV mortality during the 3 years of follow-up (16). There is no data in the literature regarding the impact of CA-IMT on CV outcomes in isolated PD population. In the current study, baseline CA-IMT was not associated with new CV events in whole population. However, new CV event rate was higher in patients with CA-IMT higher than median values and treated with PD more than two years. Additionally, new CV event rate was higher in progressors.

Table II: Comparison of parameters between progressors and nonprogressors.

	< 0.0062 mm/month progression (n=37)	≥ 0.0062 mm/month progression (n=15)	p
Age (years)	51 ± 12	48 ± 16	0.550
Male (%)	35.1	40.0	0.741
Diabetes (%)	16.2	6.7	0.361
History of CVD (%)	8.1	6.7	0.860
Body surface area (m^2)	1.75±0.21	1.77±0.15	0.800
Time on PD (months)	35.6 ± 29.0	40.2 ± 40.0	0.646
Automatized PD (%)	18.9	6.7	0.267
Mean arterial blood pressure (mmHg)	91.28 ± 14.94	95.01 ± 16.57	0.433
Pulse pressure (mmHg)	42.67 ± 12.48	48.06 ± 14.58	0.185
Total Kt/V urea	2.50±0.53	2.42±0.42	0.638
Total CCr (L/1.73m2/week)	75.50±34.11	78.86±32.65	0.761
Anuria (%)	25.0	33.3	0.543
Ultrafiltration	1119.9 ± 474.7	1285.8 ± 567.5	0.286
Residual urine volume	604.1 ± 771.9	583.5 ± 670.8	0.928
Glucose (mg/dl)	109.17 ± 41.56	97.60 ± 13.13	0.298
HbA1c (%)	5.2 ± 0.7	4.9 ± 0.5	0.116
CRP (mg/dl)	1.1 ± 1.8	2.0 ± 2.4	0.141
Total cholesterol (mg/dl)	219.6 ± 33.7	210.1 ± 26.1	0.333
Triglyceride (mg/dl)	129.1 ± 27.9	116.4 ± 24.5	0.130
LDL cholesterol (mg/dl)	230.2 ± 86.2	181.4 ± 97.8	0.081
Albumin (g/dl)	3.9 ± 0.3	4.0 ± 0.4	0.575
P (mg/dl)	4.4 ± 0.9	4.8 ± 0.9	0.201
CaxP (mg/dl)	42.1 ± 10.0	45.1 ±9.9	0.333
PTH (mg/dl)	445.7 ± 390.7	536.5 ± 423.5	0.473
Baseline CA-IMT (mm)	0.64 ± 0.17	0.57 ± 0.17	0.196

* Follow-up parameters were calculated as the time-averaged

CVD: Cardiovascular Disease, **PD:** Peritoneal Dialysis, **CCr:** Creatinine Clearance, **CRP:** C-Reactive Protein, **LDL:** Low Density Lipoprotein, **P:** Phosphorus, **CaxP:** Calcium-Phosphate Product, **PTH:** Parathyroid Hormone, **CA-IMT:** Carotid Artery Intima-Media Thickness

Progression rate of CA-IMT was found as 0.015 ± 0.053 mm/year in healthy individuals in a meta-analysis including 13 clinical trials (17). In the studied population, progression rate of CA-IMT was 0.033±0.086 mm/year. This finding supports the presence of accelerated atherosclerosis in dialysis patients.

In a small study including 47 PD patients, CA-IMT increased significantly after one-year follow-up period with a progression rate as 0.098±1.17 mm/year (18). It has been shown that body mass index, serum calcium, IL-6, TNF-alpha and CRP levels were higher in progressors compared to the non-progressors. Only age was found as independent predictor for progression of CA-IMT. In our population, progression rate of CA-IMT were lower compared to the mentioned study. Different population characteristics such as ethnicity and management of patients may be responsible for this.

We did not evaluate progression of CA-IMT according to positivity between the baseline and second measurement values, because progression of CA-IMT can be seen in healthy individuals in course of time. We thought that the assessment of CA-IMT progression was more appropriate according to presence of 0.0062 mm/month CA-IMT progression identified as a determinant of CV events. Although the progressors were more likely to be male, anuric, had longer time on PD, higher blood pressure, pulse pressure, CRP, phosphorus, calcium-phosphate product and PTH and lower CCr, residual urine volume and baseline CA-IMT compared to the nonprogressors, the difference was not significant. We could not find a predictor for progression of CA-IMT.

Our study has some limitations. The number of patients and CV events during follow-up was lower. The mean glucose load of fluids during peritoneal dialysis was not calculated. The variability in prescription of drugs during follow-up period made the analysis of drugs impossible. Interobserver variability of CA-IMT could not evaluate. Nevertheless, data from published research showed that the measurement of CA-IMT is highly reproducible (19).

CONCLUSION

In our patient group, we found that in the higher CA-IMT group, frequency of new CV events were higher in patients with longer time on PD. When we have taken into consideration progression, new CV events developed more in the group with higher progression of CA-IMT. Consecutive assessment of atherosclerosis progression by CA-IMT measurement has importance for prediction of new CV events in PD patients.

Conflict of Interest

EO is a member of scientific board of Fresenius Medical Care, Turkey. The other authors declare no conflict of interest.

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