RESEARCH ARTICLE / Araştırma Makalesi

Microalbuminuria is Not A Risk Factor for Restenosis for Patients with Below The Knee Artery Disease and Critical Limb İschemia Underwent Endovascular Therapy

Mikroalbuminüri, Kritik Uzuv İskemisi Sebebi İle Diz Altı Arterlere Uygulanan Endovasküler Tedavide Restenoz İçin Risk Faktörü Değildir

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Abstract

Objective The aim of this study was to determine whether microalbuminuria (MA) is predictive of restenosis in patients with below the knee artery (BTK) disease and treated with endovascular therapy (EVT). **(Sakarya Med J, 2018, 8(2):247-253)**

Materials and Methods We retrospectively identified patients from May 2012 to September 2016 at our clinic with severely diseased BTK arteries successfully treated by endovascular approach and measured MA recently before intervention. All patients had ankle-brachial index (ABI) measured before and after the intervention, and regular clinical follow-up with Duplex ultrasonography performed at 1 month, 6 months and 1 year. Patients underwent peripheral angiography if needed.

Results 46 patients with BTK arteries critical stenosis or occlusion treated with endovascular therapy and measurement of MA (through three months before intervention) in our institute were included. Patients were divided into two groups with MA and normoalbuminuria (MANS). There were 8 restenosis in the MA group (63.6% patency rate) and 5 restenosis in the MANS group (77.3 % patency rate) at 1 year ($p=0.517$). A statistically significant increase in the ABI (MA before 0.45±0.11 vs. after 0.89±0.08 $p<0.01$ MANS before 0.43±0.10 vs. after 0.89±0.07 $p<0.01$) and improvement in Rutherford staging ($p<0.01$) was noted in both groups following intervention.

Conclusion MA is not a predictive factor for restenosis or amputation rate in patients with BTK arterial disease treated with endovascular therapy

Keywords Microalbuminuria; drug eluting balloon; peripheral arterial disease; peripheral intervention; restenosis

Öz

Amaç Bu çalışmanın amacı mikroalbuminürinin dizaltı arterler hastalığı olan hastalara yapılan endovasküler girişim tedavisi sonrası restenozda öngörüsel olup olmadığıdır. **(Sakarya Tıp Dergisi, 2018, 8(2):247-253).**

Gereç ve Yöntem Çalışmamıza retrospektif olarak Mayıs 2012 ve Eylül 2016 tarihleri arasında dizaltı arterlerinde ciddi darlık veya tıkanıklıkları olan ve başarılı olarak endovasküler yöntem ile tedavi edilmiş ve yakın zaman içinde mikroalbuminüri (MA) değerleri ölçülmüş hastalar tanımlandı. Bütün hastalarda işlem öncesi ve sonrası ayak bileği/brakiyal indeks (ABI) değerlendirilmek ile birlikte, düzenli klinik takipte 1, 6, ve 12. Ayda duplex ultrasonları yapıldı. Ultrason sonuçlarına göre gerekli görülen hastalarda periferik anjiyografi yapıldı.

Results Kliniğimizde dizaltı arterlerinde ciddi darlığı veya tıkanıklığı olan ve mikroalbuminürisi ölçülmüş (işlemden 3 ay öncesine kadar sürede) endovasküler yaklaşım ile tedavisi yapılmış 46 hasta çalışmaya dahil edildi. Hastalar mikroalbuminürisi olup olmamasına göre 2 gruba ayrıldı (MA grup, MANS=mikroalbuminüri olmayan grup). MA grubunda 8 restenoz (63.6 % primer açık kalım oranı), MANS grubunda 5 restenoz (77.3 % primer açık kalım oranı) gözlendi. ABI' de iki grupta da istatistiksel olarak önemli artış görülmek ile birlikte (MA işlem öncesi 0.45±0.11, işlem sonrası 0.89±0.08 $p<0.01$ MANS işlem öncesi 0.43±0.10, işlem sonrası 0.89±0.07 $p<0.01$), Rutherford sınıflamasında da istatistiksel olarak önemli iyileşme ($p<0.01$) gözlendi.

Sonuç MA, dizaltı arterlerinde kritik darlık veya tıkanıklığı olan ve endovasküler yaklaşım ile tedavi edilmiş hastalarda ampütasyon oranı veya restenozu öngörmemektedir.

Anahtar Kelimeler Mikroalbüminüri; ilaç kaplı balon; periferik arter hastalığı; periferik girişim; restenoz

Introduction

Coronary artery disease (CAD) and peripheral arterial disease (PAD) have been a major public health and medical concern in both developed and developing countries[1]. Renal function is associated with either CAD or PAD development[2,3]. EVT is increasingly being used as the preferred method of revascularization in patients with BTK arterial disease. However, re-intervention after clinical restenosis is associated with increased morbidity and mortality rates[4]. Previous studies have suggested that MA might be an important risk factor of PAD[5,6]. In the present study, our aim is to determine whether MA is predictive of restenosis in patients with BTK disease and treated with EVT.

Patient population

It was a retrospective study of 46 patients who were admitted to our hospital for BTK artery lesion treatment. EVT was performed by an experienced cardiologist according to the Trans-Atlantic Inter- Society Consensus II (TASC II) guideline recommendation[7]. The inclusion criteria were the presence of critical limb ischemia (CLI, Rutherford class 4 or greater), stenosis or occlusion of at least 1 tibial vessel and MA measured recently (3 months before intervention). MA was defined as a urinary albumin/creatinine ratio of >30 mg/g[8]. Patients are divided into two groups whether MA (MA group) is seen or not seen (MANS group). All patients at our institution undergo baseline physical examinations with a focus on detecting manifestations of lower limb ischemia, classified according to Rutherford and Becker. Demographic measures were similar between the two groups (Table 1).

Table 1: Baseline Characteristics

Variable		MA (n=23)	MANS (n=23)	p
		n (%)	n (%)	
Age (Year)	Mean±SD	65.83±11.50	62.65±10.79	0.340
Gender	Male	18 (78.3)	17 (73.9)	1.000
	Female	5 (21.7)	6 (26.1)	
Diabetes mellitus		18 (78.3)	15 (65.2)	0.841
Hypertension		18 (78.3)	17 (73.9)	1.000
Hypercholesterol-aemia		16 (69.6)	17 (73.9)	1.000
Current smoker		11 (47.8)	11 (47.8)	1.000
Coronary artery disease		16 (69.6)	15 (65.2)	1.000

MA: Microalbuminuria group, MANS: Normoalbuminuria group

Statistical analysis:

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. Data were reported as mean, standard deviation, median, frequency and ratio. Student's t test was used for the comparison of normally distributed parameters. Mann Whitney U test was used for the comparison of non-normally distributed parameters. Fisher's exact test and Yates' continuity correction test were used for comparison of qualitative data. Wilcoxon signed ranks test was used to test the difference between before intervention and postintervention values. Log Rank test was used to compare patency rate between groups. The results were evaluated in 95% confidence interval and at a significance level of $p<0.05$.

Methods:

The present study complies with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee and consent was obtained from all patients for participation in the study. MA was measured in all patients in a period of 3 months before intervention. Before the procedure, all patients underwent preoperative ultrasound evaluation to visualize the extension and morphology of the BTK lesion. BTK calcifications were evaluated and quantified firstly with Doppler USG and after with digital subtraction angiography (DSA) before intervention. The ankle-brachial index was measured before and the day after the intervention before discharging the patient. Ipsilateral antegrade femoral approach was used in 40 patients whereas contralateral femoral approach was used in 6 patients. Diagnostic angiography was performed after the introducer sheath was inserted (Figure1A, B). In chronic total occlusions we used crossing catheters (Figure 1C). We prefer drug eluting balloon (DEB, single trademark used) angioplasty in BTK lesions, therefore all lesions predilated before treatment with DEB. In case of flow-limiting dissection another prolonged dilation of up to 3 minutes was performed. Drug-eluting coronary stents were planned to be used as bailout where we needed none. A completion angiogram concluded the procedure (Figure 1D). Femoral access site managed with digital pressure. All patients were discharged with 3 months dual antiplatelet therapy consisting of aspirin (100mg per day) and clopidogrel (75 mg per day) and continued with aspirin alone after 3 months. Proper medication for risk factors such as coronary artery disease, hypertension and hyperlipidemia (especially statins) were given after intervention. Patency during follow-up was evaluated with Duplex USG and with angiography performed when indicated. A peak systolic velocity ratio of 2.5 is threshold for duplex criteria for binary stenosis. The primary endpoint of this study was to compare primary patency rate and secondary endpoint is to compare major and minor amputation rate between MA and MANS group after 1 year.

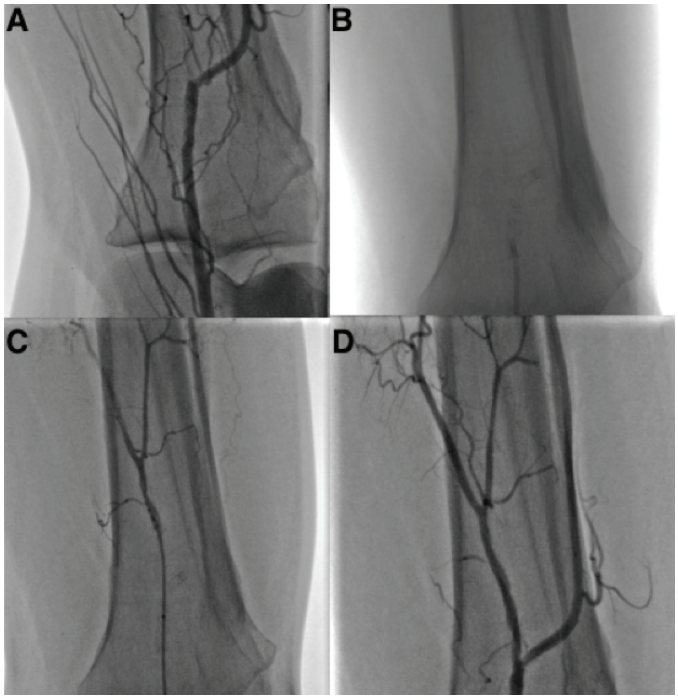

Figure 1

Figure 1 Preinterventional angiogram of a chronic total occlusion of the tibioperoneal trunk (A). Previously stent deployed to distal popliteal artery and osteal anterior tibial artery (B). Chronic total occlusion is passed with the support catheter (C). Final angiography (D)

Definitions

Restenosis is defined as >%50 critical lesion. MA was defined as a urinary albumin/creatinine ratio of >30 mg/g [8]. Major amputation was defined as limb loss above the metatarsal level, whereas minor amputation referred to trans metatarsal amputation or removal of more distal parts of the lower extremity.

Results:

The median follow-up in MA group was 13.7±3.4 months, and in MANS group was 14.0±3.5 months. Procedural characteristics are summarized in Table 2. The primary endpoint is restenosis rate at one year. After a 12 months follow-up there were 8 cases of restenosis in the MA group (60.9% patency) and 5 in the MANS group (73.9% patency) (Table 3). These 13 high-grade restenosis were documented by clinical investigation and ultrasound, and repeat angiography was performed in these cases after diagnosis. These restenosis were successfully treated by repeat PTA. There were four minor amputations in MA group (17.4 %) and three minor amputations in MANS group (13.0 %, p=1.000). There were no perforations and two cases of access-related hematoma occurred (1 in the MA group, 1 in the MANS group), which resolved on digital pressure. There was a statistically significant improvement of Rutherford stage (12 months p< 0.01) and ABI was noted in both groups (Table 4). 2 patients died (MA 1 Acute Myocardial Infarction (AMI), MANS group 1 non-cardiac mortality) in both groups.

Table 2: Procedural Characteristics

Variable		MA (n=23)	MANS (n=23)	p
		n (%)	n (%)	
Mean length (mm)	Mean±SD	111.7±26.5	110.0±25.3	0.941
Total occlusion		18 (78.3)	17 (73.9)	1.000
Severe calcification		12 (52.2)	11 (47.8)	1.000
Multiple DEB used		10 (43.5)	9 (39.1)	1.000
BTK (ATA)		11 (47.8)	13 (56.5)	0.944
BTK (PTA)		12 (52.2)	10 (43.5)	0.841

BTK: Below the knee, ATA: Anterior tibial artery, PTA: Posterior tibial artery, DEB: drug eluting balloon MA: Microalbuminuria group, MANS: Normoalbuminuria group

Table 3: Clinical Endpoints (at one year)

Variable	MA	MANS	p
	n (%)	n (%)	
Primary patency	14 (63.6)	17 (77.3)	0.517
All cause mortality	1 (4.3)	1 (4.3)	1.000
Major amputation	0 (0)	0 (0)	
Minor amputation	4 (17.4)	3 (13.0)	1.000

MA: Microalbuminuria group, MANS: Normoalbuminuria group

Discussion:

Studies showed that MA was a strong and independent risk factor for cardiovascular diseases such as PAD and CAD. In a study a 3.01 mg/g increment in albumin conferred a 5.9% increase of major cardiovascular events[9]. There are some hypotheses explaining for the association between atherosclerosis and MA. First one is that vascular endothelial damage can cause atherosclerosis and MA and the second one is presence of MA is a marker for more severe or diffuse atherosc-

lerosis[10,11]. In another study albuminuria was associated with PAD, but not carotid plaque. Due to these studies we have chosen MA as an independent risk factor for evaluation of clinical outcomes after PAD interventions in our study.

Table 4: Clinical and hemodynamic improvement

		MA		MANS	p
ABI Index	**Before procedure**	0.45±0.11		0.43±0.10	**0.541**
	After procedure	0.89±0.08		0.89±0.07	**0.941**
		p 0.001**		**p 0.001****	
	Difference	0.44±0.09		0.46±0.11	**0.617**
Preop Rutherford Becker Classification		**0,1**	0 (0)	0 (0)	
		2,3	0 (0)	0 (0)	
		4,6	23 (100.0)	23 (100.0)	
12 months follow up Rutherford Becker Classification		**0,1**	10 (45.5)	10 (45.5)	
		2,3	12 (54.5)	12 (54.5)	
		4,6	0 (0)	0 (0)	
		p 0.001**		**p 0.001****	

ABI ankle-brachial index, MA: Microalbuminuria group, MANS: Normoalbuminuria group

Endovascular treatment of BTK lesions is challenging and moreover the efficacy of angioplasty with standard balloons is limited by the high 12-month restenosis and target lesion revascularization rates in multiple studies and even limited with DEB angioplasty in one study[12-14]. Evaluation of independent factors for restenosis may affect peripheral vascular interventionists for choosing different techniques or using adjuvant new devices. Therefore we investigated if MA is an independent risk factor for restenosis in patients with BTK disease treated with EVT.

Patients with CLI, especially those with diabetes mellitus, commonly present with long, diffuse arteriosclerotic disease in the BTK region. Although 2017 European Society of Cardiology guidelines on the diagnosis and treatment of peripheral arterial diseases recommended surgery as first place in these patient cohort, these patients are often not suitable surgical candidates due to concomitant disease and advanced age, making EVT preferable[15]. Moreover TASC steering committee and the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology recommended EVT as first approach in patients with CLI and BTK disease[7]. EVT with standard balloons had lower primary patency rates compared to DEB angioplasty in multiple studies[12, 16]. Due to this we preferred DEB angioplasty for treating BTK lesions in our institute. In the present study risk factors for peripheral artery disease were found to be comparable in those with and those without MA. Although microalbuminuria is a marker for macrovascular and microvascular diseases in diabetics, relationship with coronary in stent restenosis is still controversial[17,18]. In a study it is suggested that microalbuminuria of AMI patients is associated with EPC dysfunction, which aggravates coronary remodeling which may affect in-stent restosis[19]. Moreover endothelial cell and microvascular dysfunction related to MA may also contribute to augmented neointimal formation[20]. In or study we did not find any statistically significant association between restenosis of BTK angioplasty and amputation rate with microalbuminuria, which may suggest that restenosis and the progression of naturally occurring atherosclerosis have different

pathophysiologic bases.

Mean Rutherford Becker Class was significantly decreased after a follow-up of 12 months, which reflected the outcome of intervention, is good in both groups. Another issue which affected RBC as important as intervention was the wound care which most of the patients were received in one wound center with 2 different physicians (MA group N=19, MANS N=18).

Limitations:

Number of patients and 1-year follow up was inadequate to allow statistically significant differences to be detected between the two groups. Other two limitations are routine control angiographic evaluation should be required to confirm the actual clinical impact of additional BTK angioplasty and the absence of measurement of toe brachial index (TBI). A reliable diagnosis of PAD requires the use of both ABI and TBI measurements in this patient cohort[21].

Conclusion:

MA is not a predictive factor for restenosis or amputation rate in patients with BTK arterial disease treated with endovascular therapy. Studies with larger population are needed to evaluate the predictability of MA for restenosis in this patient cohort.

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