



ENDOVASCULAR REVASCULARIZATION OUTCOMES IN PERIPHERAL ARTERIAL DISEASE PATIENTS WITH TYPE-II DIABETES MELLITUS

TİP II DİYABET TANILI PERİFERİK ARTER HASTALARINDA ENDOVASKÜLER REVASKÜLARİZASYON SONUÇLARI

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ÖZET

Giriş: Tip 2 diabetes mellitus, periferik arter hastalığı için güçlü bir predispozan faktör ve aynı zamanda endovasküler revaskülarizasyon tedavisinin başarısı için önemli bir risk faktörüdür. Tip 2 diabetes mellituslu hastalarda endovasküler revaskülarizasyonda hasta seçimi çok önemlidir.

Yöntemler: Tip 2 diabetes mellitus tanılı elli yedi hastaya endovasküler alt ekstremité revaskülarizasyonu uygulandı. Takip süresi 6 aydı ve sonuçlar işlem sonrası bir ve altı ayda iki kez kaydedildi. Hedef damar restenozu ile ilgili bağımsız faktörleri belirlemek için çok değişkenli analiz yapıldı.

Bulgular: Çalışma grubunun yaş ortalaması 66,5 yaş olup hastaların %21,2'si kadındı. Sigara içme oranı %59,6 idi. On altı hastaya stent anjiyoplasti ve kırk bir hastaya balon anjiyoplasti uygulandı. 1 aylık ve 6 aylık hedef damar açıklık oranları sırasıyla %93 ve %64,9 bulundu. Çok değişkenli analiz, tip 2 diabetes mellituslu hastalarda endovasküler revaskülarizasyon sonuçları için sigara içmenin negatif bir göstere olduğunu ve balon anjiyoplasti ve insülin bazlı tedavinin pozitif göstergeler olduğunu gösterdi.

Sonuç: Endovasküler revaskülarizasyon, tip 2 diyabetli periferik arter hastalığı olan hastalar için umut verici bir seçenektir. Bununla birlikte, aktif olarak sigara içmek ve stent anjiyoplasti, endovasküler tedavi başarısı için risk faktörleridir ve insülin bazlı tedavi ve balon anjiyoplasti, daha iyi sonuçlarla ilişkilidir.

Anahtar Kelimeler: Balon anjiyoplasti, Diabetes mellitus, Periferik arter hastalığı.

ABSTRACT

Introduction: Type 2 diabetes mellitus is a strong predisposing factor for peripheral arterial disease, it is also a significant risk factor for endovascular revascularization treatment success. Patient selection is critical in endovascular revascularization for patients with type 2 diabetes mellitus.

Methods: Fifty-seven patients with type 2 diabetes mellitus underwent endovascular lower limb revascularization. The follow-up time was 6 months and the outcomes were recorded two times in one and six months after the procedure. Multivariate analysis was run to determine independent factors that related to target vessel restenosis.

Results: Mean age of the study cohort was 66.5 years and 21.2% of patients were female. The smoking rate was 59.6%. Sixteen patients underwent stent angioplasty and forty-one patients underwent balloon angioplasty. 1-month and 6-month patent target vessel rates were found 93% and 64.9% respectively. Multivariate analysis showed that smoking is a negative indicator, and balloon angioplasty and insulin-based therapy are positive indicators for endovascular revascularization outcomes in patients with type 2 diabetes mellitus.

Conclusion: Endovascular revascularization is a promising option for peripheral arterial disease patients with type 2 diabetes. However, actively smoking and stenting may be risk factors for endovascular treatment success and insulin-based therapy and balloon angioplasty related to improved outcomes.

Keywords: Balloon angioplasty, Diabetes mellitus, Peripheral arterial disease.

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Gönderim tarihi: 10.08.2023 **Kabul tarihi:** 07.10.2023

Atıf: Kaya İÇ, Bulut Hİ. Endovascular Revascularization Outcomes In Peripheral Arterial Disease Patients With Type-II Diabetes Mellitus. Eskisehir Med J. 2023; 4(supp): 232-236. doi: 10.48176/esmj.2023.138.

INTRODUCTION

Peripheral arterial disease (PAD) affects more than 200 million people in the world. That prevalent cardiovascular disorder is associated with fatal complications such as critical limb ischemia and cardiac death. PAD is related to several cardiovascular risk factors such as smoking, hypertension, and diabetes mellitus. Diabetes mellitus is not only a risk factor for PAD occurring. It also affects the treatment success; it constitutes 70% of all ischemic-related lower extremity amputations in the US. Therefore, determining the optimal management strategy for PAD patients with diabetes is critical for patients and cardiovascular practitioners (1-5).

In this study, factors related to endovascular revascularization treatment success in patients with type 2 diabetes (T2DM) and its outcomes were investigated and discussed with the current literature.

METHODS

Study Design

This retrospective study aims to identify potential risk factors associated with early restenosis in patients with T2DM treated with endovascular therapy. The study population consisted of PAD with T2DM who underwent endovascular therapy, scanned from the electronic health records of the same hospital.

Ethical Approval

This retrospective study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the hospital clinical trials and ethics committee. The data used in this study were collected from medical records and were de-identified to protect patient confidentiality. The ethical approval number is "ESH/GOEK 2022/9".

Patients and Data Collecting

In this retrospective study, 57 patients with T2DM with femoropopliteal and aortoiliac PAD who underwent endovascular treatment between 2020-2022 were included. The data of the patients were collected with the help of the national electronic medical record system. As data, age, gender, coronary artery disease, hypertension, smoking status, insulin therapy status and the treatment method used (self-expandable bare stent, drug-eluting balloon) were collected, and the results were collected in 6 categories as stenosis, cardiovascular hospitalization, revascularization during 2 separate follow-ups as 1-month results and 6-month results. All patient data was de-identified and transferred to the database to maintain confidentiality. The database was reviewed for this study.

Endovascular Procedure

Interventions were performed by a single interventionist in one angiography laboratory, using a Canon Infinix-I INFX 8000-V single-plane Toshiba angiography system on a movable interventional table. Each patient was routinely given 300 mg of clopidogrel orally before the procedure. Seventy to 100 U/kg of unfractionated heparin were injected intra-arterially to maintain the activated clotting time of >200 seconds. Patients, in a supine or prone position according to the puncture point, were placed into the appropriate field of view by a manually controlled sliding table. A posterior-anterior projection was routinely used. An oblique projection

was occasionally used to confirm the presence of stenosis and/or evaluate the result of angioplasty. Magnification was used only occasionally, mostly in below-the-knee interventions, at the discretion of the interventionist. A 7F sheath was used in all therapeutic interventions. Lesion predilation with an uncoated balloon was consistently performed. The size and length of the paclitaxel drug-eluting balloons (DEB), which determine the total drug load, were chosen referring to a ruler placed behind the patient's leg; diameter sizing was 1:1 to the reference vessel. The DEB was inflated for at least 120 seconds from 10 mm proximal to 10 mm distal to the target lesion; in requiring lesions >1 balloon, a 5-mm balloon overlap was allowed to obtain a uniform drug elution in the treated vessel. Self-expandable stent implantation was performed in progressive stenosis or if a dissection flap was seen in the control after balloon dilation. In therapeutic interventions with a retrograde approach, digital subtraction angiography (DSA) was performed through a pigtail catheter. The Iohexol contrast medium of 350 mg/mL (Omnipaque 350, GE HealthCare, Ireland) was manually injected into the arterial system by the interventionist. On average, 100 mm³ (175 mg/ml) of contrast medium was used for the patients who underwent aortoiliac therapeutic interventions.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were reported as mean, depending on the distribution of the data. Categorical variables were reported as percentages. The primary outcome of the study was 6-month restenosis in target vessels. Categorical variables age, gender, smoking status, insulin therapy status, ischemic heart disease, hypertension, and the treatment method used (self-expandable bare stent, drug-eluting balloon) was evaluated with multivariate analysis in terms of relationship with primary outcome. The p-value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Our study cohort's mean age was 66.5 years and 21.1% (n=12) of patients were female. The group was majorly consisting of actively smoker patients, and that rate was found 59.6% (n=34). Cardiovascular comorbidities were also high in the study cohort, ischemic heart disease prevalence was 63.2% and hypertension prevalence was 64.9%. All of the patients had T2DM diagnosis and 61.4% of them were receiving insulin-based therapy (Table 1).

Lower Limb Endovascular Revascularization

Outcomes

Sixteen patients underwent stent angioplasty after the ballooning process and forty-one patients underwent balloon angioplasty alone. The first month after the procedure, only two patients needed to undergo endovascular revascularization and the total restenosis rate was 7.0%. Six months after the procedure, the target vessel restenosis rate was 35.1%, repeat endovascular revascularization rate 19.3% and surgical revascularization requirement was 3.5% (Table 2).

Independent Predictors of Target Vessel Restenosis

We tested with logistic regression the preprocedural characteristic parameters and procedural approach to determine independent predictors of target vessel restenosis. Stent angioplasty (OR=5.08) and

Table 1. Patient's characteristics.

Parameters	Study Cohort (n=57)
Gender (female,%) (n)	21.1 (12)
Age (mean years) (n)	66.5 (57)
Active Smoker (%) (n)	59.6 (34)
Hypertension (%) (n)	64.9 (37)
Ischemic Heart Disease (%) (n)	63.2 (36)
Chronic Heart Failure (%) (n)	8.8 (5)
Insulin based therapy (%) (n)	61.4 (35)
Oral antidiabetic medications (%) (n)	38.6 (22)
Stent angioplasty (%) (n)	28.1 (16)
Balloon angioplasty (%) (n)	71.0 (41)

Table 2. Outcomes of endovascular revascularization in patients with type 2 diabetes mellitus.

Outcomes	Study Cohort
1-month stenosis (%)	7.0 (4)
1-month revascularization(%) (percutaneous)	3.5 (2)
1-month surgical revascularization(%)	0
6-month stenosis(%)	35.1 (20)
6-month revascularization(%) (percutaneous)	19.3 (11)
6-month surgical revascularization(%)	3.5 (2)

Table 3. Predictors of 6-month target vessel (Femoral Artery) restenosis.

Variable	P value	Odds Ratio	95% CI
Gender	0.261	2.86	0.458-17.930
Smoking	0.043	4.86	1.05-22.45
Hypertension	0.783	1.22	0.300-4.98
Coronary artery disease	0.661	0.73	0.178-2.995
Stent angioplasty	0.030	5.08	1.172-22.01
Insulin based therapy	0.030	0.21	0.052-863

smoking(OR=4.86) were found to be an increased risk of six-month target vessel restenosis. Insulin-based therapy

(OR=0.21) was found to be associated with lower target vessel restenosis risk (Table 3).

DISCUSSION

PAD is a condition that is known to independently predict and increase the risk of cardiovascular and cerebrovascular ischemic events, thus negatively affecting both the quality of life and survival expectancy of patients (1). Research has indicated a higher prevalence of PAD in patients with diabetes mellitus than in non-diabetic patients. Moreover, it has been found that PAD progresses more rapidly in diabetics, occurs at an earlier age, and is generally asymptomatic. The close relationship between PAD and diabetes mellitus is caused by endothelial dysfunction and chronic inflammation mechanisms (2-4). According to epidemiological projection studies, the number of patients with T2DM is expected to rise globally from 382 million in 2013 to 592 million by 2035, in association with the obesity epidemic (5). This increase suggests that many patients with T2DM-related PAD diagnoses, complex lesions, and needs for treatment will emerge in the near future (6).

Current literature suggests that diabetic burden is prevalent among PAD patients. In a study by Chow et al. published in 2023, it was found that 33% of the 57,000 patients who underwent elective endovascular intervention for PAD were diabetic (7). While this figure may appear high, Lee's study on clinically advanced PAD patients highlights the significance of diabetic control in PAD management. Lee et al. conducted a study on 86 patients with a Rutherford 6 clinical stage who underwent endovascular treatment and found that 90% of these patients were diabetic (8). A comprehensive meta-analysis published in 2019 revealed that smoking, hypertension, and hypercholesterolemia, in addition to diabetes, are major risk factors for PAD. The study also suggested that these risk factors may impact the effectiveness of treatment (9). Our cohort, which exclusively consisted of diabetic patients, exhibited a high prevalence of common risk factors for PAD. Specifically, 59.6% of patients were active smokers; 63.2% had a history of ischemic heart disease; and 64.9% were diagnosed with hypertension. These findings underscore the significant comorbidity burden and systemic, cardiovascular, and metabolic complexity of our study cohort.

The significance of maintaining optimal glycemic control in diabetic patients is well established; however, there remains a lack of consensus regarding the optimal treatment approach (6). The UK Prospective Diabetes Study (UKPDS) reported that for every 1% reduction in HbA1c, there was a 43% reduction in the risk of lower extremity amputation and lower extremity arterial disease-related mortality (10). However, studies investigating restenosis after endovascular intervention in complicated patients have primarily concentrated on drug-eluting and bare balloons and stents (11-13). Despite the relatively limited literature on glycemic control in PAD, there is a significant lack of consensus regarding the optimal approach to achieving this control. Moreover, there is a dearth of studies investigating the outcomes of peripheral revascularization in diabetic patients who receive insulin-based therapy versus those who do not. In our study, which included only patients diagnosed with T2DM, 61.4% were receiving insulin-based therapy. Interestingly, the group receiving insulin-based therapy had significantly lower rates of target vessel restenosis compared to the other group (OR=0.21,

$p=0.030$). These findings underscore the need for further investigation into the impact of insulin-based therapy on PAD outcomes. Studies investigating glycemic control independent of PAD have yielded inconsistent results with regards to the effect of insulin monotherapy versus a combination of insulin and oral antidiabetic drugs on glycemic control (14). In contrast, a UK-based study suggested that advanced age and treatment with fewer than 5 drug combinations were associated with better glycemic control (15), while Khattab et al. reported an increased probability of success for a combination of both oral antidiabetic drugs and insulin, insulin only, and oral antidiabetic drugs only treatment (16). According to the American Diabetes Association's 2019 guidelines, metformin is the preferred initial therapy for patients with cardiovascular disease, but early insulin therapy should be considered for those with HbA1c values above 10% (17). A significant issue in endovascular revascularization is the comparison of percutaneous transluminal angioplasty with or without stent implantation, for the optimization of treatment in coronary artery disease, atherosclerotic carotid artery disease, and PAD (18). While it is conventionally believed that balloon angioplasty is the safer method for revascularization in PAD, recent studies have also suggested stent implantation as a viable option (19-22). However, our findings align with the traditional view and demonstrate that stent implantation is an independent risk factor for target vessel restenosis (OR=5.08, $P=0.030$).

We also want to emphasize that the endovascular outcomes were promising even in patients with T2DM. In our study's secondary outcomes were found acceptable in terms of revascularization outcomes. In a study conducted by Chen et al., involving 4706 complicated PAD patients, consisting of 3209 open surgical bypass and 1497 endovascular revascularization patients, the 30-day reintervention rate was reported as 5.2% and 5.1%, respectively (24). The 30-day reintervention rate in our cohort was found 3.5. Furthermore, our six-month follow up results were comparable with the literature, according to a randomized controlled study by Rosenfield et al., patients who underwent drug-eluting balloon angioplasty had a 12-month patency rate of 65.2%, while those who underwent standard balloon angioplasty had a patency rate of 52.6%, with varying levels of diabetes were around 40% in both groups (25). In our group, which consisted entirely of diabetic patients, the patency rate at six months was found to be 64.9%, and only 22.8% of total patients underwent repeated revascularization. These results demonstrate endovascular approaches are a strong option for patients with PAD, even with well-known risk factors such as T2DM and smoking.

Study Limitations

This study has several limitations that should be taken into consideration when interpreting the results. The most significant limitation is the small sample size, which means that the findings may not be applicable to larger populations. Additionally, the retrospective nature of the study introduces selection bias, which could potentially affect the validity of the results. In light of these limitations, it is important to emphasize the need for large-scale randomized controlled studies to determine the optimal revascularization strategy

for PAD patients with T2DM and indicate risk factors of treatment failure.

Conclusion

Endovascular revascularization is a promising option for patients with peripheral arterial disease and type 2 diabetes nevertheless it is important to carefully consider the various risk factors and treatment options when determining the optimal approach for each individual patient. In this study, actively smoking was found to be a risk factor for target vessel stenosis. Another factor that can impact the success of endovascular treatment in patients with type 2 diabetes is the use of stenting. While stenting can be effective in certain cases, it is important to note that it is associated with a higher risk of restenosis compared to balloon angioplasty alone. In addition, insulin-based medications might improve endovascular treatment outcomes. Further research is needed to better understand the best practices for endovascular treatment in this patient population and to identify strategies for improving outcomes and reducing complications.

Ethics Committee Approval: Eskisehir City Hospital Local Ethics Committee approved this study (ESH/GOEK 2022/9).

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

Authorship Contributions: Idea/Concept: ICK, HIB, Design: ICK, HIB, Supervision: ICK, HIB, Data collection or Processing: ICK, HIB, Analysis or Interpretation: ICK, HIB, Literature Search: ICK, HIB, Writing: ICK, HIB, Critical Review: ICK, HIB, References and Fundings: -Materials: -

Conflict of interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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