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Original article

Predictive Parameters of Arteriovenous Fistula Maturation for Hemodialysis in Patients with Diabetes Mellitus

Radojica Stolić[1], Marija Milić[2], Vekoslav Mitrović[3], Bratislav Lazić[2], Suzana Milutinović[4], Snezana Lazić[2], Kristina Bulatović[2], Vladimir Mitrović[2], Andrijana Karanović[2], Sanja Jovanović[2]

[1]*1University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia*
[2]*University of Pristina temporarily seated in Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia*
[3]*University of East Sarajevo, Faculty of Medicine Foča, Department of Neurology, Foča, Republic of Srpska, Bosnia and Herzegovina*
[4]*Academy of Educational and Medical Vocational Studies, Department of Ćuprija seated in Kruševac, Serbia*

SUMMARY

Introduction/Aim. Arteriovenous fistula (AVF) is recommended as the ideal vascular access for hemodialysis (HD), however, there are conflicting opinions when it comes to patients with diabetes mellitus (DM). The aim of the paper was to determine the predictive parameters of AVF maturation for HD in patients with DM.

Methods. The investigation was organized as a retrospective, descriptive-analytical study. The target group of our research involved 209 patients with DM, in whom AVF was created for HD. We recorded demographic and gender characteristics, location and type of AVF at the time of creation, type of anastomosis, data on the initial (a)function of the fistula, HD catheter placement, and blood pressure. Before the operation, Doppler ultrasound of the blood vessels was performed, and intraoperatively, the lumen of the artery and vein used to form the AVF was measured. We analyzed laboratory variables that were routinely controlled in our institution.

Results. Diabetics with successful maturing fistula significantly more often had proximally located AVF (p = 0.004), end-to-side anastomosis type (p = 0.036), and initial function (p = 0.001). In a univariate analysis, the brachiocephalic location of AVF (p = 0.004), end-to-side type of anastomosis (p = 0.039), and initial function of AVF (p = 0.001) were the predictive parameters of AVF maturation. Multivariable statistical analysis showed that brachiocephalic localization of AVF (p=0.021), end-to-side anastomosis type (p = 0.004), and initial function of AVF (p = 0.001) are the predictive parameters of AVF maturation in diabetics.

Conclusion. Predictive parameters of fistula maturation, in patients with DM in our study, are the initial function of AVF, brachiocephalic location, and end-to-side anastomosis.

Keywords: **arteriovenous fistula, hemodialysis, diabetes mellitus, maturation, predictive parameters**

Corresponding author:
Radojica Stolić
e-mail: radsto@ptt.rs

INTRODUCTION

In 2021, 529 million people were living with diabetes worldwide. By 2050, more than 1.31 billion people are projected to have diabetes (1).

Among the numerous health consequences of diabetes mellitus, one of the microvascular complications is diabetic nephropathy, which is chronic, progressive, and irreversible and leads to end-stage renal disease. However, it should be emphasized that in the early stages of diabetic nephropathy (stage I, stage II, and partially stage III), microvascular changes are less pronounced (2).

From the options offered, arteriovenous fistula is the most preferred option of vascular access for chronic hemodialysis and it is designated by guidelines and initiatives as the "best" available vascular access for hemodialysis. However, even though many authors have such a view, there are opposing opinions, because diabetes mellitus may be associated with arteriovenous fistula failure, most likely due to atherosclerosis, which is more pronounced in patients with diabetes, with a wide range of vascular lesions, making it difficult to establish vascular access. Diabetes is often accompanied by hyperlipemia, hypoalbuminemia, and high blood coagulation, which also leads to arteriovenous obstruction. Also, due to hemodynamic effects, the vein near the anastomotic stoma is struck by blood flow, leading to inner membrane injury, platelets, and fiber deposition, causing vascular intimal hyperplasia and stenosis (3, 4).

Yet, Gordon et al. (5) advocate the use of arteriovenous fistula in patients with diabetes, emphasizing its benefits despite various complications that may arise.

Anyway, the ultimate goal of angioaccess surgery is functional, mature, and durable access with a low complication rate. The downside is that there are many complications, mainly related to thrombosis when the arteriovenous fistula is applied, so complications such as thrombosis of vascular access remain the main problem for many patients with kidney failure, especially as a consequence of diabetes mellitus (6).

The aim of the study was to determine the predictive parameters of maturation of an arteriovenous fistula for hemodialysis, in patients with diabetes mellitus.

METHODOLOGY

The study was organized as a retrospective, descriptive-analytical study at the Clinic for Nephrology and Dialysis of the University Clinical Center in Kragujevac, Serbia.

Over a fifteen-year period, we created arteriovenous fistulas in 1,202 patients for the treatment of end-stage renal failure. The target group of our interest consisted of 209 subjects who, as the etiology of renal failure, had diabetes mellitus.

Among them, there were 148 (70.8%) subjects with a mature arteriovenous fistula, and 61 (29.2%) subjects had an immature fistula.

Maturation of arteriovenous fistulas was defined as access use for effective dialysis using two needles for 75% or more dialysis sessions over four weeks (7). A fistula is mature when it can be, nine months after arteriovenous fistula creation, routinely cannulated with two needles and delivered a minimum blood flow (typically 350–450 ml/min) for the total duration of dialysis, usually 3–5 h for high efficiency hemodialysis (8).

From our database, we recorded the demographic and gender characteristics of the patients, the location of the arteriovenous fistula (distally or proximally located), information on whether the arteriovenous fistula was created before starting hemodialysis, the type of anastomosis (end-to-side or end-to-end), information on hemodialysis catheter placement, systolic and diastolic blood pressure components, mean arterial blood pressure, and data on the initial (a)function of the fistula. In all subjects, the lumen of the artery and vein was measured intraoperatively for arteriovenous fistula formation. Likewise, we recorded the preoperative use of Doppler ultrasound. An ultrasound examination was performed on a Shimadzu SDU-2200, Tokyo, Japan, using Doppler B mode ultrasonography and a 7.5 MHz resolution probe.

We analyzed laboratory variables (erythrocytes, leukocytes, hemoglobin, platelets, albumins, glucose, uric acid, calcium, phosphorus, cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, fibrinogen), which were performed before surgery, which are routinely controlled in our institution for all hospitalized patients and which, according to our experience, would affect the maturation of the arteriovenous fistula for hemodialysis.

The study was approved by the Ethics Committee of the Clinical Center Kragujevac, by the Helsinki Declaration for Medical Research.

Statistical methods

The data were analyzed using SPSS for Windows, version 19. The level of statistical significance was set at $p \leq 0.05$. The variables were described using relative numbers, central tendency, and variability measures. The Mann-Whitney test and the Chi-square test were used to evaluate differences in the parameters under investigation. To examine associations of independent variables of interest with arteriovenous fistula maturation among diabetic patients, we performed a multivariable logistic regression analysis of factors associated with arteriovenous fistula maturation in the univariate regression analysis.

RESULTS

The study comprised 209 hemodialysis patients diagnosed with diabetes mellitus. The majority of patients–142 (67.9%) were male, and the average age of the patients was 60.77 ± 10.77 years (mean standard deviation-SD). Females were on average 63 ± 61.08 years old, while males were on average 62 ± 60.8 years old. Mature fistulas were recorded in 148 (70.8%) subjects, proximally located (brachiocephalic) fistulas were observed in 134 (64.1%) subjects, 175 (83.7%) patients had end-to-side anastomosis, and 108 (51.7%) subjects had arteriovenous fistulas created after the start of hemodialysis. Doppler was performed in 105 (50.2%) patients, and a central venous catheter was placed in 89 (42.6%) patients. The initial function of the arteriovenous fistula was recorded in 142 (67.9%) patients, while in 67 (32.1%) subjects the arteriovenous fistula was a primary failure.

Diabetics with a functional arteriovenous fistula significantly more often had a proximally located arteriovenous fistula (brachiocephalic), end-to-side type of anastomosis, and initial function of the arteriovenous fistula (Table 1).

In a univariate analysis, the brachiocephalic location of arteriovenous fistula ($p = 0.004$), end-to-side type of anastomosis ($p = 0.039$), and initial function of arteriovenous fistula ($p = 0.001$) were predictive parameters of arteriovenous fistula maturation (Table 2).

Multivariable statistical analysis showed that brachiocephalic localization of arteriovenous fistula ($p = 0.021$), end-to-side type of anastomosis ($p = 0.004$) and initial function of arteriovenous fistula ($p = 0.001$) are the predictive parameters of arteriovenous fistula maturation in diabetics (Table 3).

Table 1. *Sociodemographic and clinical characteristics of the subjects*

Variables		Matured AVF n (%) = 148 (70.8)	Immature AVF n (%) = 61 (29.2)	p-value
		Mean ± SD	Mean ± SD	
Age		60.94 ± 11.13	60.34 ± 9.91	0.468
Gender n (%)	Male	105 (73.9)	37 (26.1)	0.147
	Female	43 (64.2)	24 (35.8)	
ESR		65.76 ± 35.23	63.87 ± 37.60	0.754
RBC		3.15 ± 0.44	3.24 ± 0.49	0.364
WBC		8.72 ± 3.19	8.29 ± 2.50	0.456
HGB		92.51 ± 12.29	92.75 ± 17.42	0.609
PLT		235.10 ± 80.54	250.77 ± 88.1	0.239
Alb		33.54 ± 6.89	31.94 ± 7.22	0.113
Glu		7.50 ± 3.46	7.24 ± 3.48	0.565
Uric acid		424.99 ± 112.86	433.46 ± 141.93	0.935
Ca		2.10 ± 0.26	2.10 ± 0.21	0.891
PO_4		1.71 ± 0.54	1.61 ± 0.56	0.100
Systolic blood pressure (mmHg)		158.35 ± 30.60	154.17 ± 28.35	0.193
Diastolic blood pressure (mmHg)		86.80 ± 25.55	80.34 ± 12.24	0.239
MEAN blood pressure (mmHg)		106.12 ± 21.84	107.88 ± 23.90	0.978
Cholesterol		5.01 ± 2.25	4.85 ± 1.91	0.909
Trig		2.18 ± 1.23	2.21 ± 1.34	0.987
HDL		0.98 ± 0.36	1.10 ± 0.43	0.232
LDL		3.07 ± 1.99	3.08 ± 2.18	0.855
Fibrinogen		5.29 ± 2.47	5.03 ± 1.49	0.880
Intraoperative vein diameter (mm)		2.28 ± 0.30	2.28 ± 0.45	0.550
Intraoperative artery diameter (mm)		2.40 ± 0.41	2.31 ± 0.53	0.649
Location of AVF n (%)	Radiocephalic	44 (58.7)	31 (41.3)	*0.004
	Brachiocephalic	104 (77.6)	30 (22.4)	
Type of anastomosis n (%)	E-S	129 (73.7)	46 (26.3)	*0.036
	E-E	19 (55.9)	15 (44.1)	
Central vein catheter insertion n (%)	Yes	60 (67.4)	29 (32.6)	0.352
	No	88 (73.3)	32 (26.7)	
Type of fistula about the time of creation n (%)	After starting HD	76 (70.4)	32 (29.6)	0.884
	Before starting HD	72 (71.3)	29 (28.7)	
Doppler n (%)	Yes	75 (71.4)	30 (28.6)	0.884
	No	73 (70.2)	31 (29.8)	
Initial (a) function of AVF, n (%)	Yes	131 (92.3)	11 (7.7)	*0.001
	No	17 (25.4)	50 (74.6)	

AVF-arteriovenous fistula; SD-Std. deviation; ESR-erythrocyte; ESR- erythrocyte sedimentation rate; RBC-red blood cell; WBC-white blood cell count; HGB-hemoglobin; PLT-platelet count; Alb-albumin; Glu-glucose; Ca-calcium; PO_4-phosphate; Trig-triglycerides; HDL-high density lipoprotein; LDL-low density lipoprotein; AVF-arteriovenous fistula; E-S-termino-lateral; E-E-termino-terminal; HD-hemodialysis; *statistically significant value

Table 2. *Results of a univariable regression analysis*

Variables	B	p	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Gender	0.460	0.149	1.584	0.848	2.957
Age	-0.005	0.716	0.995	0.968	1.023
ESR	-0.001	0.769	0.999	0.989	1.008
RBC	0.431	0.202	1.539	0.793	2.985
WBC	-0.048	0.357	0.953	0.861	1.056
HGB	0.001	0.912	1.001	0.980	1.023
PLT	0.002	0.235	1.002	0.999	1.006
Alb	-0.033	0.164	0.968	0.924	1.013
Glu	-0.023	0.618	0.977	0.893	1.070
Uric acid	0.001	0.679	1.001	0.998	1.003
Ca	0.074	0.907	1.076	0.315	3.672
PO_4	-0.368	0.240	0.692	0.375	1.279
Systolic blood pressure	-0.005	0.450	0.995	0.984	1.007
Diastolic blood pressure	-0.017	0.131	0.984	0.963	1.005
MEAN blood pressure	0.004	0.685	1.004	0.987	1.021
Cholesterol	-0.037	0.663	0.964	0.815	1.139
Trig	0.018	0.905	1.018	0.763	1.358
HDL	0.701	0.288	2.016	0.553	7.351
LDL	0.003	0.984	1.003	0.778	1.292
Fibrinogen	-0.061	0.545	0.941	0.771	1.147
Intraoperative vein diameter	-0.038	0.947	0.963	0.314	2.949
Intraoperative artery diameter	-0.488	0.297	0.614	0.245	1.535
Location of AVF	-0.893	*0.004	0.409	0.222	.756
Type of anastomosis	0.795	*0.039	2.214	1.040	4.715
Central vein catheter insertion	-0.285	0.353	0.752	0.413	1.371
Type of fistula in relation to the time of creation	-0.044	0.884	0.957	0.527	1.738
Doppler	0.060	0.844	1.062	0.585	1.928
Initial (a)function AVF	3.556	0.001	35.027	15.343	79.962

Reference variable: Functional AVF; AVF-arteriovenous fistula; SD-Std. Deviation; ESR-erythrocyte; ESR-erythrocyte; RBC-red blood cell; WBC-white blood cell count; HGB-hemoglobin; PLT-platelet count; Alb-albumin; Glu-glucose; Ca-calcium; PO_4-phosphate; Trig-triglycerides; HDL-high density lipoprotein; LDL-low density lipoprotein; HD-hemodialysis; *statistically significant value

Table 3. *Results of a multivariable regression models*

Variables in the equation	B	P value	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Location of AVF (radiocephalic vs. brachiocephalic)	1.194	*0.021	3.301	1.197	9.104
Type of anastomosis (E-S vs. E-E)	-1.760	*0.004	0.172	0.052	0.571
Initial (a)function AVF (primary failure vs. initial function)	4.550	*0.001	94.661	28.892	310.147
Constant	2.429	0.125	11.343		

Reference variable: Functional AVF; AVF arteriovenous fistula; E-S -termino-lateral; E-E-termino-terminal; *statistically significant value

DISCUSSION

Arteriovenous fistulas are still the Achilles heel of modern-day hemodialysis. Beyond any doubt, a long-lasting arteriovenous fistula improves the quality of life and reduces morbidity among patients with end-stage renal disease (9). The definition of arteriovenous fistula maturation is challenging. Arteriovenous fistulas should allow the use of two needles, have adequate blood flow for the specific patient, and have minimal recirculation. The 2019 updated vascular access guidelines suggest that AVF maturation should be based on clinical judgment (10). Diabetes mellitus and its associated atherosclerosis effectively narrow the lumen of blood vessels and reduce the blood flow, thereby limiting utilization as an effective conduit. The effect of diabetes mellitus on arteriovenous fistula maturity rates is debatable. Among nephrologists, there are conflicting views, i.e., there is evidence both for and against the influence of diabetes mellitus on the maturation of arteriovenous fistula for hemodialysis (11, 12).

Due to these contradictions, with this research, we set ourselves the task of determining whether among patients with diabetes mellitus, who need an arteriovenous fistula for hemodialysis, some parameters could predict the success of functioning and maturation of the fistula. We found that the determinants of arteriovenous fistula maturation, most important to better understand and predict arteriovenous fistula maturation in our diabetic patients, were not associated with laboratory variables, but with the characteristics of the fistula itself. The result of our research showed that none of the biochemical analysis variables had statistically significant values, in the correlation of subjects with and without maturation of arteriovenous fistulas for hemodialysis, which could perhaps indicate the uniformity of the studied population.

With regards to the association between gender variation and arteriovenous fistula non-maturation, there have been conflicting results reported in the reference literature. Several studies suggested a significant correlation between female gender and decreased patency rates in arteriovenous fistulas, as well as prolonged maturation time before the fistula can be used adequately to sustain hemodialysis sessions. A combination of female gender and increased age (> 65) is significantly associated with non-maturation when compared to men of the same age group (8), probably because of smaller vessel diameters (13). Conte et al. (14) and Salmela et al. (15) found that diabetic patients had significantly lower patency rates, and also female sex and thrombophilia were associated with decreased primary fistula patency rates. Conversely, Sedlacek et al. (16) reported that diabetes was not associated with arteriovenous fistula maturation, and it did not affect either the prevalence of arteriovenous fistula creation in the diabetic group.

Historically, certain patient characteristics have been associated with poor rates of arteriovenous fistula maturation, particularly in females, the elderly, and patients with diabetes mellitus. Our subjects who had a functional fistula and patients who did not have fistula were of the same age, an average of 60 years, thereby eliminating bias. In our study, there were no age differences between male and female patients. Gender differentiation was on the men's side, namely, more than half of the total number of patients were men, and in the group of respondents who had matured fistula, more than two-thirds of the patients were men. However, there were no differences in gender distribution between the two groups, so the gender distribution did not have a decisive influence on fistula maturation in our investigation.

Primary failure, or initial failure of arteriovenous fistula function occurs within 72 hours of surgery when the fistula either thromboses before use or is unsuitable for use. In this study, we used functional maturation, which was defined as access to efficient dialysis using two needles for 75% or more of dialysis sessions over four weeks (17). The meta-analysis by Rooijens et al. (18) showed a pooled estimated primary failure rate of 15.3%, with a tendency to a higher risk of primary failure and a lower primary patency rate when other parameters are evaluated, such as gender, positioning of the arteriovenous fistula in the upper arm, patients with diabetes, etc.

The results of our research, among patients with diabetes mellitus, determined that the initial afunction of arteriovenous fistulas (32%) is twice as high compared to the rate reported by Rooijens et al. (18). The results of our research, among patients with diabetes mellitus, determined that the initial afunction of arteriovenous fistulas (32%) was as twice as high compared to the rate reported by Rooijens et al. (18). Likewise, our results showed that the primary function of the arteriovenous fistula had

a predictive capacity for maturation, which supports the necessity of planning the start of hemodialysis with a mature fistula.

The highest arteriovenous fistula patency was observed in patients with brachiocephalic arteriovenous fistula. These findings may be attributed to the difference in the diameter of the inflow artery (19). Farrington et al. (20) importantly underscored that vascular diameters demonstrated a linear association with arteriovenous fistula maturation with no clear threshold values. The increasingly common choice of creating arteriovenous fistulas with the larger arteries of the upper arm is in line with these findings. Based on the results of 265 arteriovenous fistulas created in patients with diabetes mellitus, Janeckova et al. concluded that initial arteriovenous fistula surgery at the elbow may be a better option than that at the wrist (21).

Intraoperatively measured lumens in our subjects did not significantly affect the rate of fistula maturation, and our study groups did not differ significantly in this variable. On the other hand, the majority of our subjects had brachiocephalic fistulas, which were statistically significantly different from patients with radiocephalic fistulas. What is particularly important for our research is that brachiocephalic fistula has predictive significance for functioning and maturation. Thus, it seems that the diameter of blood vessels used for anastomosis is more important during maturation and that diabetes has an additive role in determining fistula patency.

Surgical technique is of paramount importance for long-term patency of arteriovenous fistula. There are two commonly known techniques to carry out the anastomosis between the veins to the artery: end to side and side to side. Some studies concluded that the side-to-side configuration showed early maturation and higher cumulative patency rates (22). A generally acceptable attitude is that an end-to-side anastomosis is the most recommended, while the end-to-end connection is only used for the reconstruction or primary but emergency access (23). End-to-end anastomosis yields higher rates of hand ischemia, especially in diabetic and elderly patients. Yet, it is currently advised that the method of arteriovenous fistula creation should be selected based on the individual patient's vessel anatomy (24).

Regardless of the recommendations, opinions, or findings in the literature, we had had the experience with the use of end-to-side anastomoses in the majority of our subjects, especially due to the morphological characteristics of the artery walls, which, in most cases, are atherosclerotically altered. This type of anastomosis, in our subjects, showed statistically significant differences between patients with and without functional maturation of the fistula. Moreover, end-to-side anastomosis has shown its importance in the prediction of fistula maturation.

Limitation

As this was a retrospective analysis of our cohort, we were unable to actively recruit further patients to increase the sample size, which can make it difficult to generalize the conclusions to the entire population, although we had relatively uniform results when it comes to the demographic and gender characteristics of the respondents. We tried to stratify the sample as far as this type of study allowed, but were not sure that all the confounding factors were eliminated. Likewise, unfortunately, we did not have information on the type of diabetes mellitus, which, again, could affect the achieved results.

CONCLUSION

Predictors of maturation of arteriovenous fistula for hemodialysis in our study, among the population of patients with diabetes mellitus, are initial fistula function, brachiocephalic location, and terminolateral type of anastomosis.

Future studies, with a well-stratified sample, should demonstrate the influence of metabolic parameters on arteriovenous fistula maturation.

Conflict of interest

The authors declared no conflicts of interest concerning the authorship and/or publication of this article.

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Prediktivni parametri maturacije arteriovenske fistule za hemodijalizu kod bolesnika sa dijabetesom melitusom

Radojica Stolić[1], Marija Milić[2], Vekoslav Mitrović[3], Bratislav Lazić[2], Suzana Milutinović[4], Snežana Lazić[2], Kristina Bulatović[2], Vladimir Mitrović[2], Andrijana Karanović[2], Sanja Jovanović[2]

[1]*Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra interne medicine, Kragujevac, Srbija*
[2]*Univerzitet u Prištini sa privremenim sedištem u Kosovskoj Mitrovici, Medicinski fakultet, Kosovska Mitrovica, Srbija*
[3]*Univerzitet u Istočnom Sarajevu, Medicinski fakultet Foča, Odsek za neurologiju, Foča, Republika Srpska, Bosna i Hercegovina*
[4]*Akademija vaspitačko-medicinskih strukovnih studija, Odsek medicinskih studija Ćuprija, Kruševac, Srbija*

SAŽETAK

Uvod/Cilj. Arteriovenska fistula (AVF) preporučuje se kao idealan vaskularni pristup za hemodijalizu (HD). Međutim, postoje oprečna mišljenja kada su posredi bolesnici sa dijabetesom melitusom.
Cilj ove studije bilo je određivanje prediktivnih parametara sazrevanja AVF-a za hemodijalizu kod bolesnika sa dijabetesom melitusom.
Metodologija. Istraživanje je organizovano kao retrospektivna, deskriptivno-analitička studija. Ciljnu grupu našeg istraživanja činilo je 209 bolesnika sa dijabetesom melitusom, kojima je kreiran AVF za hemodijalizu. Evidentirali smo demografske i polne karakteristike, lokaciju i tip AVF-a u odnosu na vreme kreiranja, vrstu anastomoze, podatke o početnoj funkciji, odnosno odsustvu funkcije fistule, postavljanju katetera za hemodijalizu i vrednostima krvnog pritiska. Pre operacije urađen je dopler ultrazvuk krvnih sudova, a intraoperativno su mereni lumen arterije i vene koje su korišćene za kreiranje AVF-a. Analizirali smo laboratorijske varijable koje se rutinski kontrolišu u našoj ustanovi.
Rezultati. Osobe sa dijabetesom sa uspešno sazrelim fistulama značajno češće imale su proksimalno lociran AVF (p = 0,004), termino-lateralni tip anastomoze (p = 0,036) i inicijalnu funkciju (p = 0,001). U univarijantnoj analizi, brahiocefalični AVF (p = 0,004), termino-lateralni tip anastomoze (p = 0,039) i početna funkcija AVF-a (p = 0,001) bili su prediktivni parametri sazrevanja AVF-a. Multivarijantna statistička analiza pokazala je da su brahiocefalna lokalizacija AVF-a (p = 0,021), termino-lateralna anastomoza (p = 0,004) i inicijalna funkcija AVF-a (p = 0,001) prediktivni parametri sazrevanja AVF-a kod osoba sa dijabetesom.
Zaključak. Kao prediktivni parametri sazrevanja fistule kod bolesnika sa dijabetesom melitusom u našoj studiji izdvojili su se početna funkcija AVF-a, brahiocefalične lokacije i termino-lateralni tip anastomoze.

Ključne reči: **arteriovenska fistula, hemodijaliza, dijabetes melitus, sazrevanje, prediktivni parametri**