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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Analysis of risk factors for progression of diabetic nephropathy in patients with type 2 diabetes

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SUMMARY

Introduction/Objective The aim of the study was to examine the progression of diabetic nephropathy (DN) in a prospective three-year period as well as to establish the risk factors for DN progression.

Methods The study involved 45 patients with type 2 diabetes and DN (26 males, aged 18–62 years) followed up for three years. All the patients underwent physical examination and laboratory analysis at each visit. Laboratory analyses included complete blood count, serum glucose, urea, creatinine, protein, lipid concentration, glycosylated hemoglobin (HbA1c) and urine protein, albumin and creatinine concentration. Glomerular filtration rate (GFR) was calculated using Modification of Diet in Renal Disease formula. Kidney length and parenchymal thickness were measured by ultrasound.

Results Fasting serum glucose concentration (12.0 ± 2.79 *vs*. 9.50 ± 2.22, p < 0.001) and HbA1c (7.99 ± 1.43 *vs*. 7.49 ± 1.29, p < 0.031) were decreased over the three years. Albuminuria increased (43.75 ± 10.83 *vs*. 144.44 ± 52.70 mg/l, p < 0.001) and GFR (63 *vs*. 58.3 ml/min/1.73 m^2) decreased significantly during the study, but serum lipid concentration remained unchanged. Mean kidney length and parenchymal thickness decreased during the three years. Linear regression analysis found systolic blood pressure, fasting glycemia, HbA1c as positive and kidney length and parenchymal thickness as negative predictors of proteinuria increase, but proteinuria as negative and serum iron and albumin concentrations as positive predictors of annual change in GFR.

Conclusion High blood pressure and high HbA1c are selected as significant risk factors for increasing proteinuria, which is a significant predictor of GFR decreasing in patients with DN.

Keywords: diabetic nephropathy; progression; risk factors

INTRODUCTION

Diabetes mellitus (DM) is a major health problem impairing the quality of life and diminishing the life expectancy of millions of people [1]. The frequency of DM is enormously increasing worldwide, thus more and more people are exposed to the risk of developing diabetic complications. Diabetic nephropathy (DN) is one of the most detrimental consequences of DM regarding patients' quality of life and survival [2]. It affects more than 20% of all diabetic patients, and due to limited therapeutic options it remains the leading cause of chronic kidney disease [3]. DN is a leading cause of end-stage kidney disease (ESKD) in developed countries. The clinical diagnosis of DN is based on the presence of albuminuria and/or reduced estimated glomerular filtration rate (GFR) in the absence of signs or symptoms of other primary causes of kidney damage [4].

International organizations have predicted epidemic proportions of DN and have anticipated that the incidence of DN will dramatically increase by 2050. In addition, DN is associated with a high cardiovascular mortality and frequent development of ESKD [5]. The prevalence of DN patients on regular dialysis in Bosnia and Herzegovina is also increasing and between 2002 and 2014 it has increased from 39.6 to 142 patients per million [6]. The only way to decrease an unceasing rise in the number of patients with DN is persistent implementation of DN prevention and regular screening. The preventive measures should be directed at the risk factors for the occurrence and progression of DN and the screening for DN should begin from the time of diabetes diagnosis as it is observed that about 7% of the patients diagnosed with diabetes already have microalbuminuria [7, 8, 9].

The aims of this study were to examine the progression of DN in a prospective three-year period as well as to establish the risk factors for DN progression.

METHODS

The study involved 45 patients with type 2 diabetes and DN including 26 males and 19 females, with the average age being 61.24 years (18–62 years). The patients were selected from a population of patients with type 2 diabetes and DN who regularly control themselves in the Outpatient Department for Internal Medicine of the University Hospital in Foča,

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both by an endocrinologist and a nephrologist. The criteria for diagnosis of DN were as follows: persistent albuminuria > 300 mg/g creatinine, existence of diabetic retinopathy, exclusion of other kidney or renal tract diseases. The patients who were successively visiting the abovementioned department and whose GFR was above 30 ml/min/1.73 m^2, were included in the study. The patients with any malignancy, serious hepatic failure, those who suffered myocardial infarction or even cerebrovascular insult in the past six months, as well as patients with any kidney disease apart from DN were not included in the study. The selected patients were followed up for three years and only those who came to the control at least once a year during those three years were included in the analysis.

All the patients were interviewed, subjected to physical examination including measuring of blood pressure and calculating body mass index (BMI) and electrocardiography. Physical examination and laboratory analyses were performed at each patient's visit. During the three-year study, we tried to achieve optimal glycoregulation and regulation of blood pressure with the use of renin–angiotensin–aldosterone system inhibitors (RAASi), considering it the basic strategy for slowing down DN progression, but we also advised patients on the importance of diet, physical activity, smoking cessation.

Laboratory analyses were performed at the Department of Biochemistry and Hematology at the Foča University Hospital and they included complete blood count, measuring of creatinine concentration by modified Jaffe method (Beckman Creatinine Analyzer II; Beckman Coulter, Inc., Brea, CA, USA), as well as concentrations of serum glucose, protein, lipid and urine creatinine determined by standard biochemical methods on biochemistry analyzer of the Abbott Laboratories, Chicago, IL, USA (Alcyon Analyzer SA). Glycosylated hemoglobin (HbA1c) is expressed as percentage and determined by using automated high-performance liquid chromatography systems. All laboratory analyses were performed at each patient's visit except serum lipid and blood protein concentrations, which were determined at the beginning and at end of the study. Also, we did not have the opportunity to regularly measure albumin in urine, but all patients underwent this analysis at the beginning of the study because it was one of the criteria for DN.

Urine proteins are expressed by the ratio of urine protein and creatinine concentration (cut off value being 20 mg/mmol). Urine albumins were measured by colorphotometric method with bromocresol green (Olympus AU 400 analyzer, Olympus Co. Ltd., Tokyo, Japan) and expressed by the ratio of albumin and creatinine concentration (cut off value being 3.4 mg/mmol).

GFR was calculated by the Modification of Diet in Renal Disease formula [10]. The progression of DN was assessed on the basis of proteinuria change during the three-year study and expressed by the difference in proteinuria values at the third and first examination. The annual change in GFR was the second indicator of DN progression calculated as the ratio of the difference in GFR at the first and the third examination, divided by the number of years between these examinations.

A kidney ultrasound examination was performed by an experienced doctor in ultrasound diagnostics on a GE LOGIQ P5 ultrasound instrument (GE Healthcare, Chicago, IL, USA) with a 3.5 MHz convex probe. Craniocaudal diameter and parenchymal thickness of the kidney were measured and expressed in millimeters.

Statistical analysis

Continuous variables are presented as the arithmetic mean and standard deviation or as a median and interquartile range depending on the characteristics of the variable, while categorical ones are presented as frequencies. Applying the Kolmogorov–Smirnov test, the type of distribution of all variables was examined. For the analysis, ANOVA with Bonferroni test, Kruskal–Wallis test, Student's t-test, Wilcoxon test and χ^2 test were used as appropriate. Linear regression analysis was used to examine the association of GFR and proteinuria change and demographic, clinical, and laboratory variables.

IBM SPSS Statistics, Version 21.0 for Windows (IBM Corp., Armonk, NY, USA) and MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium) were used for statistical analysis.

This study protocol was done in accordance with the ethical principles of the Declaration of Helsinki. All study participants gave their informed consent and the study was approved by Committee on Ethics of the Foča University Hospital (2/20).

RESULTS

Table 1 shows the main data of examined patients. The average age of the patients at the time of setting the diabetes diagnosis was 51.64 years, while the average diabetes duration was 10.13 years.

Table 1. Main data about the examined patients with diabetic nephropathy at the beginning of the study

Sex, male		26 (57.8%)
Age, years		61.24 ± 11.18
DM duration, years		10.13 ± 7.87
Age at the time of DM diagnosis, years		51. 64 ± 13.03
Type of treatment	Hypoglycemic oral agents	18 (40%)
	Insulin	12 (26.7%)
	Combined	13 (28.9%)
	Missing data	2 (4.4%)
Family history of DM, yes		22 (48.9%)
Cigarette smoking	Yes	6 (13.3%)
	Former smoker	9 (20%)
Alcohol	Yes	8 (17.8%)
Antihypertensive treatment	ACEI	35 (77.8%)
	ARB	5 (11.1%)
	ACEI + CCB	5 (11.1%)

Results are presented as numbers (%) or as mean ± standard deviation; ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CCB – calcium channel blockers

Table 2. Changes in laboratory parameters, body mass index, and blood pressure in the three-year-long study

Laboratory parameters	1 initial visit	2 after 19.8 ± 2.1 months	3 after 37.7 ± 2.7 months	p		
				1–2	2–3	1–3
Fasting serum glucose, mmol/l	12 ± 2.79	11.9 ± 2.06	9.5 ± 2.22	0.014	0.068	< 0.001
HbA1c %	7.99 ± 1.43	7.81 ± 1.32	7.49 ± 1.29	0.241	0.003	0.031
BMI, kg/m^2	28.47 ± 4.14	29.05 ± 4.4	27.76 ± 4.05	0.156	0.004	0.002
Systolic BP, mmHg	146.44 ± 24.18	141.67 ± 22.21	136.55 ± 12.52	0.144	0.336	0.017
Diastolic BP, mmHg	85.78 ± 9.83	83.44 ± 8.97	82.38 ± 6.56	0.211	0.618	0.038
Urea, mmol/l	8.2 ± 4.3	10.57 ± 6.29	10.22 ± 6.77	0.008	0.698	0.060
Creatinine, µmol/l	98 (88.0–118.5)	100 (84–162)	92.5 (79–129)	0.043	0.939	0.343
GFR, ml/min/1.73 m^2	63 (52–80)	56 (40–85)	58.3 (38.0–89.8)	0.365	0.306	0.030
Erythrocytes × 10^{12}/l	4.28 ± 0.58	4.2 ± 0.69	4.0 ± 0.39	0.770	0.009	0.004
Hemoglobin, g/l	127.5 ± 19.58	120.2 ± 21.96	115.82 ± 14.52	0.015	0.023	< 0.001
Albumins, g/l	36.09 ± 5.65	–	35 ± 4.37	–	–	0.142
Proteins, g/l	63.77 ± 7.24	–	63.5 ± 6	–	–	0.881
Total cholesterol, mmol/l	5.91 ± 1.55	–	5.66 ± 1.31	–	–	0.283
Triglycerides, mmol/l	2.33 ± 0.9	–	2.34 ± 1.03	–	–	0.856
HDL cholesterol, mmol/l	0.9 ± 0.26	–	0.96 ± 0.43	–	–	0.334
LDL cholesterol, mmol/l	3.97 ± 1.38	–	3.76 ± 1.22	–	–	0.244

Data are expressed as mean ± standard deviation or as median and interquartile range; statistical significance of the difference was calculated using Student's t-test and Wilcoxon test;
HbA1C – hemoglobin A1C; BP – blood pressure, HDL – high-density lipoprotein; LDL – low-density lipoprotein; BMI – body mass index

Table 3. Changes in albuminuria, proteinuria, kidney length, and parenchymal thickness in the patients with diabetic nephropathy over three years

Laboratory parameters	1 initial visit	2 after 19.8 ± 2.1 months	3 after 37.7 ± 2.7 months	p		
				1-2	2-3	1-3
U-albumin, mg/l	43.75 ± 10.83	144.44 ± 52.7	–	< 0.001	–	–
U-protein, g/day	0.39 (0.18-1.1)	0.78 (0.44-1)	0.5 (0.27-1.1)	0.006	0.449	0.040
P/Cr, mg/mmol	96.2 (33-152)	143 (59.3-313.9)	136.6 (66.0-352.9)	0.013	0.001	0.039
Right kidney length, mm	117 ± 5.16	114.53 ± 6.61	113.7 ± 7.54	0.007	0.030	0.002
Right kidney parenchymal thickness mm	16.31 ± 2.43	15.63 ± 2.34	15.22 ± 2.22	0.178	0.418	0.037
Left kidney length, mm	118.48 ± 4.61	114.24 ± 18.64	115.94 ± 7.54	0.119	0.523	0.004
Left kidney parenchymal thickness, mm	17.05 ± 3.19	16.31 ± 3.04	15.88 ± 2.57	0.283	0.471	0.046
Mean kidney length, mm	117.88 ± 3.95	115.83 ± 6.07	114.85 ± 7.14	0.010	0.032	0.001
Mean kidney parenchymal thickness, mm	16.79 ± 2.79	16.18 ± 2.75	15.71 ± 2.17	0.299	0.381	0.042

Data are represented as mean ± standard deviation or as median and interquartile range; statistical significance of the difference was calculated using Student's t-test or Wilcoxon test

The patients regularly visited their family physicians, and they visited a nephrologist twice a year. Table 2 shows the values of the monitored parameters recorded on nephrologist examinations at the beginning of the study, in the middle of the study, i.e. after about 18 months, and at the end of the study. Fasting serum glucose concentrations and HbA1c values were above the recommended limit during all three years, although at the very beginning of the study these values were significantly higher than after three years (HbA1c: 7.99 ± 1.43 *vs.* 7.49 ± 1.29, $p < 0.031$). The BMI of patients increased during the first 18 months, and then BMI decreased significantly. Systolic and diastolic blood pressure decreased significantly over the three years. All the patients were on antihypertensive therapy and 77.8% of them used angiotensin-converting enzyme inhibitors, 11.1% angiotensin II receptor blockers, and 11.1% angiotensin II receptor blockers plus calcium channel blockers. There were no changes in the type of antihypertensive drugs during the follow-up but their doses have been changing according to blood pressure values.

During the first 18 months of the study, serum concentration of urea and creatinine increased significantly. The median GFR decreased from 63 ml/min/1.73 m^2 to 58.8 ml/min/1.73 m^2 over the three years and the difference was significant (Table 2).

Albuminuria increased from 43.75 ± 10.83 mg/l to 144.44 ± 52.70 mg/l ($p < 0.001$) and proteinuria from 0.39 g/day to 0.78 g/day ($p = 0.006$) between the first and the second examination, but proteinuria changed insignificantly until the end of the study (Table 3). Kidney length and parenchymal thickness decreased and the dimensions measured at the beginning and end of the study differed significantly.

Table 4 shows the results of linear regression analysis in which the dependent variable was the difference in proteinuria measured at the end and at the beginning of the study, and the independent variables all demographic, clinical, and laboratory variables. Due to the relatively small group and the collinearity among some variables, several models were used in this analysis. Only those variables that are statistically significantly associated with proteinuria change are shown. The analysis identified systolic blood pressure and fasting glycemia at the end of the study as well as HbA1c measured at the second examination as positive

Table 4. Factors associated with the difference in proteinuria at the end and at the beginning of the study.

Parameters	B	p	95% CI
Systolic blood pressure 3, mmHg	6.05	0.049	0.29–12.80
Kidney length 3, cm	-22.05	0.003	-35.98–-8.12
Parenchymal thickness 1, mm	-83.65	0.038	-162.13–-5.16
Fasting plasma glucose 3, mmol/l	72.61	0.024	10.13–135.08
HbA1c % 2	114.75	0.043	4.14–225.35

Table 5. Factors associated with annual change in glomerular filtration rate in patients with diabetic nephropathy (multivariate linear regression analysis)

Parameters	B	p	95% CI
P/Cr 2, mg/mmol	-0.04	0.002	-0.072–-0.02
Iron, mmol/l	1.55	0.007	0.47–2.64
Albumins 2, g/l	1.3	0.032	0.12–2.47

predictors and kidney length at the end of the study and parenchymal thickness at the beginning of the study as negative predictors of difference in proteinuria.

Univariate linear regression analysis was used to select the variables associated with the annual change in GFR. Systolic blood pressure at the end of the study, kidney length and parenchymal thickness both at the beginning and at end of the study, as well as proteinuria at the beginning of the study were identified as negative predictors, while hemoglobin, albumin, and iron concentrations were selected as positive predictors of annual GFR change. These variables, which were found to be significantly associated with GFR change by univariate linear regression analysis, were combined in the multivariate analysis. This analysis identified proteinuria as negative and serum iron and albumin concentrations as positive predictors of annual change in GFR.

DISCUSSION

The main objective of this study was to determine risk factors for DN progression. The study included 45 patients with type 2 diabetes and DN who were followed up for three years. During the three-year follow-up, glycoregulation as well as regulation of hypertension improved significantly. Also, BMI decreased significantly, but serum lipid concentrations did not change. At the same time, GFR was significantly decreased, albuminuria and proteinuria increased, and even kidney length and kidney parenchymal thickness were significantly decreased. Linear regression analysis showed that proteinuria increased more over a three-year period if systolic blood pressure, fasting glycemia and HbA1c were greater and kidney length and parenchymal thickness were lesser. Univariate linear regression analysis showed that the annual decrease in GFR was significantly associated with systolic blood pressure, kidney length and parenchymal thickness, proteinuria, hemoglobin but also serum albumin and iron concentrations. Multivariate analysis identified only proteinuria as negative and serum iron and albumin concentrations as positive significant independent predictors of annual GFR change.

Two major risk factors for the occurrence and progression of DN are hyperglycemia and hypertension. Hyperglycemia is a major pathogenic factor for the occurrence of DN, and numerous studies have confirmed that intensive diabetes therapy and achieving of glycemic target values can prevent or postpone the onset of albuminuria, as well as the progression of DN [11, 12]. Early aggressive treatment of hyperglycemia seems to be important and early favorable glycemic environment is remembered so it is called "metabolic memory" [13]. In the present study, a significant decrease in both fasting glycemia and HbA1c during the three-year follow-up of patients with type 2 diabetes and DN was shown. Both of these biomarkers were also identified by linear regression analysis as predictors of worsening proteinuria. These results confirmed the results of many other studies about the importance of glycoregulation for DN progression. Particularly significant is the fact that better glycoregulation can slow down the progression of DN even if this better glycoregulation is achieved in patients who have had diabetes for many years. In patients included in our study, at the time of study inclusion, diabetes lasted 10.13 years on average, yet in 24.4% of patients, proteinuria did not increase or even decrease, and in 35.5% it increased by less than 100 mg/mmol. Linear regression analysis showed that an increase in proteinuria was associated with fasting glycemia and HbA1c, not with values at the beginning of the study but with values measured at the end of the second or the third year of the study. This indicates that if patients with diabetes lasting more than 10 years achieve better glycoregulation, proteinuria will be affected. Such results have been shown in patients with type 1 diabetes but less frequently in patients with type 2 [14].

In contrast to the association between proteinuria and glycoregulation, there are results on the effect of glycoregulation on GFR. Coca et al. [14], in a large-scale meta-analysis involving 28,065 adult patients with type 2 diabetes, found that intensive glycoregulation did not affect the increase in serum creatinine concentration or the development of ESKD. Similar to these results, our study's linear regression analysis isolated no biomarkers of glycoregulation as significant factors associated with annual GFR change. Coca et al. [14] considered that this lack of association between glycoregulation and changes in GFR was a consequence of the late detection of type 2 diabetes and DN. Therefore, at the time of detection, patients have GFR within normal limits but most probably significant pathomorphological changes in the kidneys. Our results confirmed this assumption. A significant decrease in kidney length and kidney parenchymal thickness was recorded over the course of three years. This decrease could not have happened if there were no morphological changes at the beginning of the study.

Hypertension is another significant risk factor that has been pointed out by numerous studies, and the achievement of target blood pressure has proven to be a significant measure of primary and secondary prevention of DN as well as cardiovascular diseases, the most common cause of death in diabetes [9, 15]. In most patients with type 2 diabetes, hypertension exists even before diabetes is detected.

Our study confirmed the significance of elevated blood pressure for DN progression. Systolic blood pressure at the end of the third year of the prospective study were selected as significant factor associated with both an increase in proteinuria and a decrease in GFR.

RAASi are the standard treatment in the care for hypertensive patients with DM, especially when renal involvement is present [15, 16]. RAASi, even in non-antihypertensive doses, decreased the production of profibrotic factors and directly prevented fibroblast activation [17]. Ramipril may protect the kidneys by suppressing insulin-like growth factor-1 and mitigating the accumulation of renal mesangial matrix [18]. All these findings suggest a novel therapeutic role of RAASi in slowing down of DN progression. In people with advanced chronic kidney disease, stopping renin–angiotensin–aldosterone system inhibition was associated with higher absolute risks of mortality and major adverse cardiovascular events, but also with a lower absolute risk of initiating kidney replacement therapy [19]. There are many RAASi available on the market, but a small number of papers compare the renoprotective effect of different RAASi in patients with DN [20]. Finally, a recent network meta-analysis comparing the effects of antihypertensive agents in diabetic patients with kidney disease showed that combination of fosinopril and amlodipine appeared to be the most efficacious in reducing proteinuria [21].

Although our previous studies have shown that primary care physicians know that RAASi have the greatest renoprotective effect and the greatest number of patients with diabetes and hypertension are treated with RAASi, there is insufficient insistence on achieving the target blood pressure [22]. KDOQI guidelines recommend target blood pressure ≤ 140/90 mmHg for patients with diabetes without proteinuria, while for those with albuminuria blood pressure ≤ 130/80 mmHg is recommended [23]. Our national guidelines recommend that in patients with DN, a target blood pressure lower than 130/80 mmHg may be considered appropriate, dependent on the patient's characteristics, comorbidity or response to therapy [24]. Given that our study included patients who were most commonly in their seventh decade of life and with different comorbidities, we considered blood pressure below 140/90 mmHg to be the targeted one and we achieved this in most patients during the study.

Obesity and arterial hypertension were found in a significant number of patients included in our study. The average BMI was about 27 kg/m^2. Regular check-ups during this prospective study most likely contributed to the fact that the average BMI value significantly decreased over the three years, so BMI does not appear as a significant factor associated with an increase in proteinuria, or a decrease in GFR. This confirms the well-known view that changes in diet and lifestyle, as well as physical activity, which can lead to weight loss, are significant measures of prevention of type 2 diabetes and DN [25].

Dyslipidemia is considered to be one of the factors that affect the progression of DN [26]. Although the concentrations of all four lipids controlled in our patients were higher than those recommended by the guidelines, none of these four lipids were selected as a factor associated with an increase in proteinuria or a reduction in GFR.

The importance of the present study is that, for the first time, risk factors for the occurrence and progression of DN have been examined in the Republic of Srpska and Bosnia and Herzegovina. The major disadvantage of the study is the relatively small number of patients included in the studies. In addition, to examine the progression of DN and its outcome, it would be important that the follow-up period was longer than three years, which would allow establishing not only the deterioration of kidney function but also by the occurrence of ESKD.

CONCLUSION

The study found that type 2 diabetes is discovered late, that patients are burdened with a numerous changeable and unchangeable risk factors for DN. High blood pressure and high HbA1c levels proved to be the most significant risk factors for the progression of DN, while more effective regulation of these factors slowed down its progression.

Conflicts of interest: None declared.

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Анализа фактора ризика за прогресију дијабетесне нефропатије код болесника са дијабетесом типа 2

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САЖЕТАК

Увод/Циљ Циљ рада био је да се испита прогресија дијабетесне нефропатије (ДН) у трогодишњем периоду и да се утврде фактори ризика за прогресију ДН.

Методе Студија је обухватила 45 болесника с дијабетесом типа 2 и ДН (26 мушкараца, старости од 18 до 62 године) који су праћени три године. Свим болесницима су урађени физикални преглед и лабораторијске анализе приликом сваког прегледа. Лабораторијске анализе су укључивале комплетну крвну слику, серумску глукозу, уреу, креатинин, протеине, концентрацију липида, гликозилирани хемоглобин (*HbA1c*), концентрацију протеина, албумина и креатинина у урину. Јачина гломеруларне филтрације (ЈГФ) израчуната је коришћењем формуле *Modification of Diet in Renal Disease*. Дужина бубрега и дебљина паренхима измерени су ултразвуком.

Резултати Концентрације глукозе у серуму наште (12,0 ± 2,79 *vs*. 9,50 ± 2,22, $p < 0,001$) и *HbA1c* (7,99 ± 1,43 *vs*. 7,49 ± 1,29, $p < 0,031$) смањивале су се током три године. Албуминурија се повећала (43,75 ± 10,83 *vs*. 144,44 ± 52,70 *mg/l*, $p < 0,001$) и ЈГФ се значајно смањила (63 *vs*. 58,3 *ml/min*/1,73 m^2) током студије, док је концентрација липида у серуму остала непромењена. Средња дужина бубрега и дебљина паренхима смањиле су се током три године. Линеарном регресионом анализом утврђено је да су систолни крвни притисак, гликемија наште, *HbA1c* позитивни, а дужина бубрега и дебљина паренхима негативни предиктори повећања протеинурије, док је протеинурија издвојена као негативан, а концентрација гвожђа и албумина у серуму као позитивни предиктор годишње промене ЈГФ.

Закључак Висок крвни притисак и висок *HbA1c* издвојени су као значајни фактори ризика за повећање протеинурије, која је значајан предиктор смањења ЈГФ код болесника са ДН.

Кључне речи: дијабетесна нефропатија; прогресија; фактори ризика