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SLOW PROGRESSION OF CHRONIC KIDNEY DISEASE AND WHAT IT IS ASSOCIATED WITH

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A b s t r a c t: *Introduction:* The risk factors for CKD include diabetes, hypertension, smoking, systemic inflammation, obesity, proteinuria, dislipidaemia and anaemia, as well as gender, age, ethnic minority status and positive family history. By screening and adequate treatment of modifiable risk factors we are able to prevent or delay the progression of the disease.

Aim: The aim of the study was to assess the risk factors associated with rapid progression of CKD and to see what factors are protective of slow progression.

Methods: The study is retrospective. The medical charts of 116 patients with CKD who had been followed up for several years at the Outpatient Department of the Nephrology Clinic in Skopje were analysed. Patient age ranged from 19 to 78 years. The patients were divided into two groups: fast progressors – group I (n = 82; GFR decline > 0.1 ml/min/month) and slow progressors – group II (n = 34; GFR decline =/< 0.1 ml/min/month) with an average follow-up time of 55 months. Patients with diabetic nephropathy were excluded from the study because they are known to be fast progressors. The following variables were analysed: underlying cause of CKD, gender, age, time of follow-up, initial GFR (calculated creatinine clearance according to the Cockroft&Gault formula), final GFR, systolic and diastolic blood pressure, mean and pulse blood pressure, haemoglobin, cholesterol and 24h protein excretion rate. Progression of CKD was assessed by linear regression analysis of the mean monthly decrease of calculated creatinine clearance (delta CCcr).

Results: There was no statistically significant difference between fast and slow progressors regarding their systolic, diastolic, mean and pulse arterial blood pressure. With regard to the other risk factors, it appeared that progressors are significantly younger (50.50 vs 59.20; p = 0.001, more anaemic Hb-116.68 g/l vs 123.27; p = 0.0036), more

proteinuric (1.46 g/d vs 0.76; p = 0.003) and have higher diastolic blood pressure (92.25 mmHg vs 84.75 mmHg; p = 0.005) compared to non-progressors. There was no statistical difference between the groups in terms of gender (p = 0.451). Regarding renal diagnosis, there was a statistically significant difference in progression among the four diagnostic groups, p = 0.00208. Chronic glomerulonephritis (GN) was associated with significantly faster progression (delta KKK = -0.5525 ml/min/mo) compared to interstitial nephritis/nephrosclerosis (IN/NS) (delta KKK = -0.2542 ml/min/mo), p = 0.03918, and compared to unknown renal disease (Unkn) (delta KKK = -0.1487 ml/min/mo), p = 0.0245. Polycystic kidney disease (PKD) had faster progression (delta KKK = -0.5704 ml/min/mo) compared to IN/NS, p = 0.04340 and compared to Unkn, p = 0.0251.

Conclusion. Timely recognition of risk factors for CKD progression and their treatment by correction of high blood pressure, reduction of proteinuria, correction of anaemia and dyslipidaemia (to lower cardiovascular risk) may retard progression of CKD to end-stage renal disease, thus delaying the need for renal replacement therapy.

Key words: chronic kidney disease, slow progression, risk factors, calculated creatinine clearance.

Introduction

The occurrence of chronic kidney disease (CKD) and subsequent rate of loss of renal function are highly variable among individuals with the same underlying cause of renal injury or degree of functional impairment. Individual variability of risk is typical of complex diseases and reflects the multifactorial nature of the biologic mechanisms that are involved in the underlying disease process [1]. The principal outcomes of CKD include progressive loss of kidney function leading to end-stage renal disease (ESRD) and the development and progression of cardiovascular disease (CVD) [2]. The observation that small reductions in the decline in renal function early in the disease process can provide marked benefits later, in terms of delaying progression to renal replacement therapy (RRT), suggests that substantial benefits can be gained from the early identification and treatment of individuals at risk [3]. The initial step involves the identification and modification of risk factors. The risk factors for CKD can be divided into 2 categories—clinical and sociodemographic factors. Clinical – modifiable factors for CKD include: diabetes, hypertension, smoking, systemic inflammation, obesity, proteinuria, dislipidaemia and anaemia. Sociodemographic – non-modifiable risk factors include: gender, age, ethnic minority status and positive family history [4]. By screening and adequate treatment of modifiable risk factors we are able to prevent or delay the progression of the disease.

Glomerular filtration rate (GFR) is the best measure of overall kidney function in health and in disease. A declining glomerular filtration rate (GFR)

correlates with a decline in renal function. Although many formulae have been developed to facilitate estimation of GFR, the most widely used have been those proposed by Cockcroft& Gault and, more recently, the MDRD equations based on 4-variables (Modification of Diet in Renal Disease) [5]. Physiological decline of GFR is 1 ml/min/1.73 m^2 per year at the age of 40. Every decrease above physiological is a result of kidney damage which progresses to ESRD [6]. The rate of GFR decline is highly variable among patients, ranging from slowly progressive over decades, to rapidly progressive over months. The rate of decline in GFR can be used to estimate the interval until the onset of kidney failure, and that is why continual follow-up of renal function through measurement of GFR is important [7]. In some conditions such as: hypovolaemia, use of contrasts, NSAID, nephrotoxic drugs and obstruction of the urinary tract, acute decrease of GFR may occur. It is necessary to define the factors associated with a "fast" or "slow" GFR decline and to provide aggressive treatment such as: strong glycaemic control, control of blood pressure, correction of dyslipidaemia, anaemia and obesity, and smoking cessation.

CKD is a silent medical problem that requires laboratory analysis to make an early diagnosis. Early aggressive management of *diabetes mellitus*, hypertension, and dyslipidaemia are vital. Awareness and management of the frequent complications also improve ESRD outcomes. Ongoing consultation with the nephrology team, including a renal dietician, is important for delaying disease progression and improving patient quality of life [8].

Aim of the study

The aim of the study was to assess the risk factors associated with rapid progression of CKD and to see what factors are protective of slow progression.

Materials and Methods

The study is retrospective. The medical charts of 116 patients with CKD who had been followed up for several years at the Outpatient Department of the Nephrology Clinic in Skopje were analysed. Patient age ranged from 19 to 78 years. The patients were divided into two groups: fast progressors – group I (n = 82; GFR decline > 0.1 ml/min/month) and slow progressors – group II (n = 34; GFR decline =/< 0.1 ml/min/month) with an average follow-up time of 55 months. Patients with diabetic nephropathy were excluded from the study because they are known to be fast progressors. The following variables were analysed: underlying cause of CKD, gender, age, time of follow-up, initial GFR (calculated creatinine clearance according to the Cockroft&Gault formula), final

GFR, systolic and diastolic blood pressure, mean and pulse blood pressure, haemoglobin, cholesterol and 24h protein excretion rate. Progression of CKD was assessed by linear regression analysis of the mean monthly decrease of calculated creatinine clearance (delta CCcr).

The Mann Whitney-U test was used in non-parametric analysis to compare the means between the two groups with an unequal number of statistical units for numerical variables, and X^2 test for categorical variables (Fisher – test). The Spearman rho rank test was used to determine the correlation between two continuous variables. The influence of underlying renal disease on progression of CKD was analysed by the analysis of variance (ANOVA test). Statistical significance was set at a p value of less than 0.05. Data were analysed using the Statistica software package *Statistica for Windows 6.0*.

Results

The distribution of age, follow-up period, mean value of calculated creatinine clearance, initial GFR and final GFR, haemoglobin, systolic and diastolic blood pressure, proteinuria and cholesterol in the two groups of patients are shown in Table 1.

Table 1 – Табела 1

Comparison of means for the numerical variables between the two groups of patients (fast progressors – Group I, and slow progressors – Group II)
Компарација на средните вредности од нумеричките варијабли меѓу двете групи на пациенти (брзи прогресори – група 1 и бавни прогресори – група 2)

	Group 1	**Group 2**	**p**
Age (years)	50.50 ± 12.93	59.20 =/- 11.88	0.001035*
Follow-up period (months)	49.96 ± 37.50	68.52 =/- 31.00	0.012344*
Δ CCcr (ml/min/month)	-0.4626 ± 0.45	-0.0073 ± 0.067	0.000000*
Initial CCcr (ml/min/1.73m^2)	40.30 ± 21.76	37.79 ± 15.84	0.543937
Final CCcr (ml/min/1.73m^2)	23.61 ± 16.15	37.20 ± 18.22	0.000131*
Haemoglobin (g/l)	116.68 ± 16.26	123.27 ± 12.36	0.036425*
SBP (mmHg)	150.16 ± 19.85	145.00 ± 22.69	0.225840

	Group 1	Group 2	p
DBP (mmHg)	92.25 ± 11.94	84.75 ± 15.09	0.005446*
Pulse pressure (mmHg)	57.54 ± 14.96	60.25 ± 15.42	0.381866
MAP (mmHg)	114.92 ± 12.66	110.03 ± 14.78	0.075089
Proteinuria (g/day)	1.46 ± 1.25	0.76 ± 0.70	0.003379*
Cholesterol (mmol/l)	5.40 ± 1.058	5.47 ± 1.15	0.751111

There was no statistically significant difference between the fast and slow progressors regarding their systolic, mean and pulse arterial pressure. With regard to other risk factors, it appeared that age, level of anaemia, proteinuria and diastolic blood pressure were significantly different between the two groups. Slow progressors were older, less anaemic, had lower diastolic blood pressure, had lower proteinuria, were followed for a longer period of time and had higher final creatinine clearance (because of their slow progression).

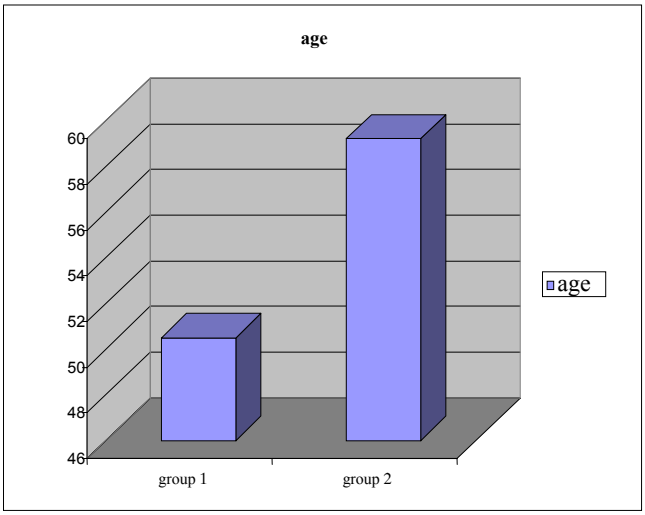

Figure 1 – Slow progressors are older than fast ones (Elderly patients progress less than younger ones)

Слика 1 – Бавни прогресори се постари пациенти во однос на брзите (постарите пациенти прогредираат побавно во однос на младите пациенти)

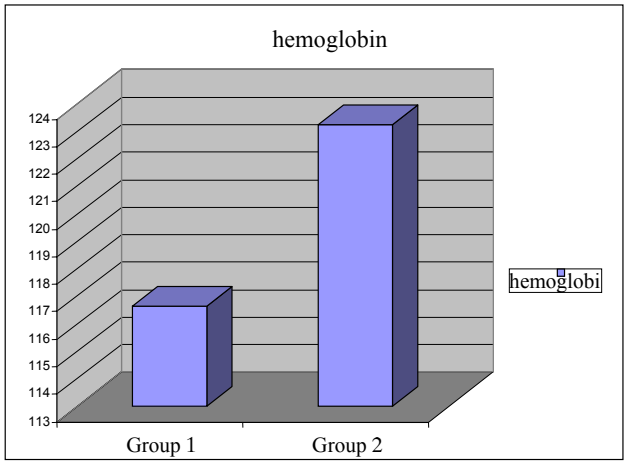

Figure 2 – Slow progressors are less anaemic than fast ones

Слика 2 – Бавните прогресори се помалку анемични во однос на брзите прогресори

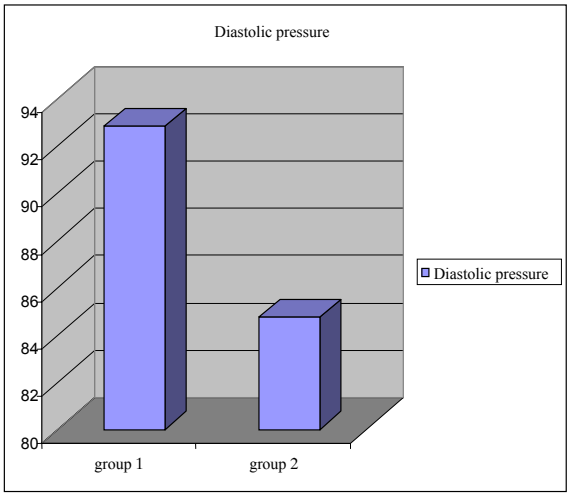

Figure 3 – Slow progressors have lower diastolic blood pressure than fast progressors

Слика 3 – Бавните прогресори имаат понизок дијастолен крвен притисок во однос на брзите прогресори

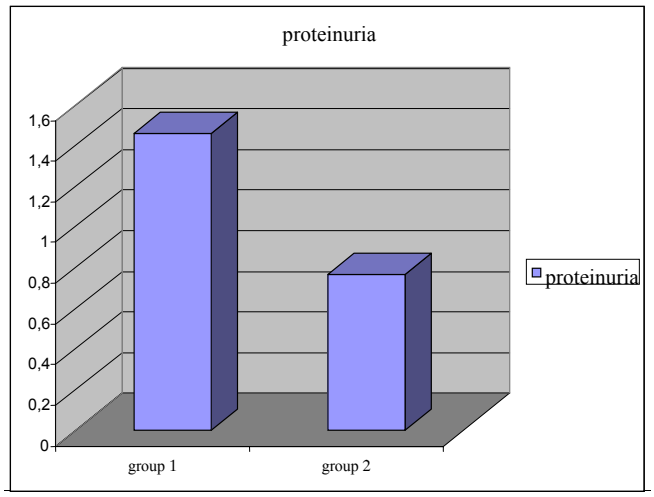

Figure 4 – Slow progressors have lower proteinuria than fast progressors
Слика 4 – Бавните прогресори имаат помала протеинурија во однос на брзите прогресори

The distribution of gender and underlying renal disease in both groups are shown in Tables 2 and 3.

Table 2 – Табела 2

Distribution of gender in both groups
Дистрибуција на пол во обете групи

	Female	Male	Fisher exact test
Group 1	39	42	0.451
Group 2	18	17	

Table 3 – Табела 3

Distribution of underlying renal disease in the two groups of patients
Дистрибуција на основното бубрежно заболување во двете групи на пациенти

Cause of CKD	Groups I	Group II
Nephroarteriosclerosis (NAS)	25.9 %	25.7%
Polycystic kidney disease (PKD)	6.2%	5.7%
Chronic Interstitial Nephritis (CIN)	39.5%	45.5%
Glomerulonephritis (GN)	29.6%	5.6%
Presence of diabetes as a comorbidity and unknown renal disease	8.7%	14.3%

The results showed that gender was not statistically different between the two groups of patients (p = 0.451) as well as the underlying renal disease. Chronic glomerulonephritis, though, (GN) was more common in the group of faster progressors.

Table 4 – Табела 4

Correlation between risk factors and mean monthly decrease of calculated creatinine clearance
Корелација меѓу ризик факторите и средниот месечен пад на калкулираниот креатинин клиренс

	Patients	Spearman	p-level
Age & Δ CCcr	116	0.404550	0.000007*
Initial CCr & Δ CCcr	116	-0.050543	0.590016
Final CCr& Δ CCcr	116	0.476406	0.000000*
Xaemoglobin & Δ CCcr	116	0.276705	0.002640*
SBP & Δ CCcr	116	-0.177764	0.056252
DBP & Δ CCcr	116	-0.366337	0.000052*
Pulse pressure & Δ CCcr	116	0.056771	0.544971
MAP & Δ CCcr	116	-0.225749	0.014826*
Proteinuria & Δ CCcr	115	-0.365219	0.000060*
Cholesterol & Δ CCcr	116	0.062942	0.502071

Table 5 – Табела 5

Mean monthly decrease of calculated creatinine clearance in different renal diseases
Среден месечен пад на калкулиран креатинин клиренс кај различни бубрежни заболувања

Type of renal disease	Δ CCcr Means	Δ CCcr N	Δ CCcr Std.Dev.
GN	-0.552500	18	0.663292
PKD	-0.570400	15	0.572943
CIN/NAS	-0.254242	66	0.320474
Undetermined	-0.148706	17	0.181569
All Grps	-0.325940	116	0.437103

Table 6 – Табела 6

Stat*istically significant differences in mean monthly decrease of calculated creatinine clearance among different renal diseases (ANOVA)*
Статистички сигнификантна разлика во средниот месечен пад на калкулиран креатинин клиренс меѓу различните бубрежни заболувања (ANOVA)

	{1}	{2}	{3}	{4}
GN {1}		0.999399	0.039184	0.024512
PKD {2}	0.999399		0.043408	0.025118
CIN/NAS {3}	0.039184	0.043408		0.786031
Undeterm {4}	0.024512	0.025118	0.786031	

Discussion

The results of the study show the association of certain risk factors with CKD progression. Both groups of patients are homogeneous by gender and initial calculated creatinine clearance. The results show that the decrease of renal function is strongly asossiated with high blood pressure, particularly the diastolic one, as well as the level of anaemia and proteinuria. The patients in group 2 were followed for a longer period of time than patients in group 1, because of the slower decrease in GFR, and hence, their final CCcr at the end of the study was higher. Data presented here show that **older age** is a protective factor for the progression of renal disease. Similar results were shown by Jungers *et al*. in their study, where the proportion of patients who started dialysis was lower in the group aged $\geq$ 75 years than in younger patients (28% vs 48%, $p < 0.02$). [9]

Haroun *et al*. presented that **higher systolic and higher diastolic BP** were associated with a relative hazard for CKD of 1.02 (95% CI 1.01–1.03) and 1.04 (95% CI 1.03–1.06), respectively, after adjustment for age, gender, smoking, and diabetes treatment ($p < 0.001$) [10]. Another prospective study of over 100,000 men and women in Japan showed that diastolic BP was the strongest predictor of the later development of end-stage renal disease, though the results were not stratified by gender [11]. In another study, Fliser *et al*. confirmed a lower GFR in patients with heart failure, but not with higher mean arterial blood pressure (MAP) [12]. In our study we confirmed that systolic blood pressure is not significantly associated with CKD progression, whereas MAP and diastolic blood pressure are ($p = 0.015$ and $p = 0.00005$).

A few studies show that **pulse pressure** is a significant prognostic factor for mortality and the appearance of CVD in patients with CKD, or patients on dialysis or after renal transplantation, but its influence on progression is

not yet proved. In our study, it appeared that it is not associated with progression of CKD ($p = 0.381$) [13].

The NHANES III study confirmed a connection between **low haemoglobin** and renal damage [14]. A Canadian cohort study of patients with CKD showed that at any level of renal impairment, the risk for progression to ESRD is increased by the presence and level of anaemia [15]. Our results are consistent with the results of other studies in respect of anaemia and its association with GFR decline ($p = 0.036$).

Hypercholesterolaemia was found to be an important independent predictor of the rate of loss of renal function. In their study Krolewski *et al*. showed that the prevalence of patients with rapid loss of renal function was racing with increasing level of serum cholesterol [16]. Unlike this, in our study we found that serum cholesterol was not associated with the decline of renal function, and both groups had a similar level of hypercholesteronemia.

Regarding renal diagnosis, patients with diabetic nephropathy (not diabetes as a comorbidity) were excluded from our study because they are known to have fast progression. Jungers *et al*. analysed retrospectively the influence of **primary renal disease** on the rate of progression of CKD. The slope of decline in delta CCcr was 2.5 times higher, as a mean, in patients with chronic glomerular disease than in patients with chronic interstitial nephritis, and 1.5 times higher than those with polycystic kidney disease or nephroarteriosclerosis. By multivariate analysis the type of nephropathy was the most significant factor affecting delta CCcr. [17]. In another study, Wight *et al*. retrospectively analysed the rate of CKD progression in 102 patients and found that patients with chronic glomerulonephritis and PKD had faster rates of progression compared with the other groups. When proteinuria and haemoglobin were taken into consideration, the rate of progression of GN was comparable to the other diseases [18]. Our results showed that patients with GN were more present in the group of fast progressors, while CIN was more present in the group of slow progressors. The GN and PKD patients in our study progressed more than twice as much as the patients with CIN and NAS.

Proteinuria had a strong positive relationship with the decline of GFR in the entire study population in the study of Jungers [17], as well as in many other studies, which was similar to our results, too. Proteinuria was significantly higher in the fast progressors compared to the slow progressors ($p = 0.0033$) and it also significantly correlated with the decline of CCcr ($p = 0.00006$).

Conclusion

To date, several risk factors have been shown to affect the progression of renal damage to ESRD. That is why timely recognition of these risk factors

and their treatment by correction of high blood pressure, reduction of proteinuria, correction of anaemia and dyslipidaemia (to lower cardiovascular risk) may retard the progression of CKD to end-stage renal disease, thus delaying the need for renal replacement therapy.

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Резиме

БАВНА ПРОГРЕСИЈА НА ХРОНИЧНА БУБРЕЖНА БОЛЕСТ И СО ШТО Е АСОЦИРАНА?

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Вовед: Во ризик факторите за хронична бубрежна болест се вбројуваат дијабетот, хипертензијата, пушењето, системската инфламација, обезноста, протеинуријата, дислипидемијата и анемијата, како и полот, возраста, етничката припадност и позитивната фамилијарна анамнеза за бубрежно заболување. Преку скрининг и адекватен третман на модифицирачките ризик фактори може да се превенира или одложи прогресијата на болеста.

Цел: Целта на студијата е да утврди кои ризик фактори се асоцирани со брза прогресија, а кои фактори се протективни кај бавна прогресија.

Методи: Студијата е од ретроспективен карактер. Беа анализирани 116 пациенти со ХББ кои беа следени неколку години преку амбулантата при Клиниката за нефрологија во Скопје. Возрасната граница на пациентите беше од 19 до 78 година. Пациентите беа поделени во 2 групи: брзи прогресори – група 1 (N = 82; намалување на ГФР > 0,1 мл/мин/месечно) и бавни прогресори – група 2 (N = 34; намалување на ГФР =/< 0,1 мл/мин/месечно) со просечно време на следење од 55 месеци. Во студијата целно беа исклучени пациенти со докажана дијабетична нефропатија, имајќи во предвид дека овие

пациенти имаат побрза прогресија во однос на пациенти со друго основно бубрежно заболување. Анализирани беа следните параметри: основно бубрежно заболување, пол, возраст, месеци на следење, почетен и краен ККК (калкулиран креатинин клиренс одредуван според Cockroft-Gault-овата формула), систолен, дијастолен и среден крвен притисок, пулсен притисок, хемоглобин, холестерол и протеинурија. Прогресијата на ХББ беше проценета со линеарна регресиона анализа на средниот месечен пад на калкулираниот креатинин клиренс (делта ККК).

Резултати: Резултатите покажаа дека не постои статистичка значителна разлика меѓу прогресорите и непрогресорите во однос на систолниот и средниот крвен притисок, пулсниот притисок и холестеролот. Во однос на другите ризик фактори се покажа дека прогресорите се сигнификантно помлади (50,50 vs. 59,20; p = 0,001), поанемични (Hb 116,68 g/l vs. 123,27; p = 0,0036), со повисока протеинурија (1,46 g/ден vs. 0,76; p = 0,003) и повисок дијастолен крвен притисок (92,25 mmHg vs. 84,75; p = 0,005) во однос на непрогресорите. Од статистичката обработка се гледа дека не постои сигнификатна статистичка разлика во однос на полот (p = 0,451) меѓу овие две групи. Во однос на основното бубрежно заболување (гломерулонефрит, полицистична бубрежна болест, интерстиционефрит, нефроартериолосклероза и недиференцирана бубрежна болест), постои сигнификантна разлика во прогресијата, p = 0,00208. Хроничниот гломерулонефрит (ХГН) сигнификантно побрзо прогредира (делта ККК = -0,5525 мл/мин/мес) во однос на интерстиционефрит/нефроартериолосклероза (ИН/НАС) (делта ККК = -0,2542 мл/мин/-мес), p = 0,03918, и во однос на недиференцирано основно бубрежно заболување (НеДиф) (делта ККК = -0,1487 мл/мин/мес), p = 0,0245. Полицистичната бубрежна болест (ПББ) побрзо прогредира (делта ККК = -0,5704 мл/мин/мес) во однос на ИН/НАС, p = 0,04340 и во однос на НеДиф, p = 0,0251.

Заклучок: Навремено откривање на ризик факторите и нивна корекција преку контрола на крвен притисок, редукција на протеинурија, корекција на анемија и дислипидемија (да го намали кардиоваскуларниот ризик) водат до забавување на прогресијата на хроничната бубрежна болест до терминален стадиум, а со тоа и одложување на потребата од ренална заместителна терапија.

Клучни зборови: хронична бубрежна болест, бавна прогресија, ризик фактори, калкулиран креатинин клиренс.

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