PharmacologyOnLine

Archives • 2021 • vol.2 • 366-377

NEPHROPROTECTIVE THERAPY AND RENAL CIRCULATION IN PATIENTS WITH DIABETIC NEPHROPATHY

Svitlana Novychenko*, Lilia Zub, Svitlana Kovalenko, Igor Zamorskii, Stanislav Roborchuk, Olga Scrynchuk

Bucovinian State Medical University Chernivtsi, Ukraine

* switlananovy70@gmail.com

Abstract

Diabetes mellitus considerably accelerates advance of chronic kidney disease (CKD) reducing glomerular filtration rate (GFR) by 12–15 ml/min per year resulting in much earlier deterioration of the renal function – at a younger age. One more important mechanism of CKD aggravation is associated with proteinuria. Continuous increase of protein content in the urine is an important symptom of kidney lesion. Albumin excretion is an important marker of diabetes mellitus. In case of CKD caused by diabetic nephropathy proteinuria is not only a sign of the disease but its important pathogenic mechanism of advancing. Arterial hypertension (AH) intensifies proteinuria and therefore accelerates CKD aggravation. Antihypertensive therapy with diabetic nephropathy is indicated not only to reduce AH but to decrease the risk of cardiovascular diseases and slow down kidney lesions. Choosing antihypertensive agents special attention should be paid to angiotensin converting enzyme (ACE) inhibitors and calcium channel-blocking agents with their typical nephroprotection, which slows down advance of chronic kidney disease.

Keywords: *nephroprotection, proteinuria, antihypertensive drugs, angiotensin converting enzyme inhibitors.*

Introduction

In spite of an etiological factor resulting in primary kidney lesion further course of the disease and its advance is characterized by common regularities of pathogenic mechanisms and stage-by-stage type. The most frequent causes promoting kidney lesions today are arterial hypertension (AH) and diabetes mellitus (DM) [1, 2,3]. Approximately 25–35 % of patients with chronic kidney disease (CKD) suffer from so-called hypertensive nephrosclerosis (in Ukraine the term "primarily contracted kidney" is more commonly used), which directly results from advanced kidney lesion with AH. One more important mechanism deteriorating kidney function with AH is quicker rate of atherosclerosis development including atherosclerosis of the renal arteries in comparison to individuals with normal level of arterial blood pressure [4,5,6]. DM considerably accelerates advance of chronic kidney disease reducing glomerular filtration rate by 12–15 ml/min per year resulting in much earlier deterioration of the renal function – at a younger age [7,9]. One more important mechanism of CKD aggravation is associated with proteinuria. Continuous increase of protein content in the urine is an important symptom of kidney lesion. Albumin excretion is an important marker of diabetes mellitus [8]. In case of CKD caused by diabetic nephropathy proteinuria is not only a sign of the disease but its important pathogenic mechanism of advancing. Arterial hypertension (AH) intensifies proteinuria and therefore accelerates CKD aggravation [10,11, 12]. The risk of cardiovascular complications and advance of kidney lesions increases in proportion to increased proteinuria [13,14,16]. Hypotensive therapy with diabetic nephropathy is indicated not only to reduce AH but to decrease the risk of cardiovascular diseases and slow down advance of kidney lesions [15, 17, 18].

Special attention in choosing antihypertensive agents should be paid to rational combination and maximal simplification of the pattern of their use due to administration of ready combined drugs[19,20]. A simple pattern to use drugs promotes increasing administration of the therapy indicated. Similar to all other antihypertensive agents ACE inhibitors cause dilation of the adductor artery, but contrary to other classes of drugs they lead to dilation of the abductor artery which considerably decreases blood pressure inside of the glomerulus[21,22]. Decrease of the hydrostatic pressure in the glomerulus results in considerable reduction of hyperfiltration and decrease or extinction of proteinuria [23,24, 25].

Objective of our research was to study the indicators of the main kidney function including glomerular filtration rate, proteinuria level and estimate disorders of lipid metabolism, lipid peroxide oxidation in patients with diabetic nephropathy (DN) using antihypertensive drugs possessing nephroprotective mechanism of action.

Methods

84 patients with type 2 diabetes mellitus aged from 47 to 75 with the duration of the disease for 10-15 years were examined at the Department of Nephrology of the Regional Clinical Hospital of Chernivtsi. All the patients were distributed between two groups: I group included 43 patients with stage 1 CKD and DN IV degree, II group included 41 patients with stage 2 CKD and DN IV degree. Every group was divided into subgroups (with stage 1 and 2 arterial hypertension (AH)). The control group included 19 practically healthy individuals. Patients in all the groups were distributed according to the age and sex.

The diagnosis and degree of DN was made according to C.E. Mogensen classification (1983) on the basis of common clinical methods of examination. Nephropathy caused by diabetes is considered to be present with macroalbuminuria available (over 300 mg) or microalbuminuria with comorbid retinopathy or the period of DM over 10 years. According to the classification DN III degree is determined with microalbuminuria from 30 to 300 mg/day, increased or normal GFR and unstable increase of arterial pressure. The diagnosis of DN IV degree is made on the basis of proteinuria (more than 500 mg/day), normal or moderately reduced GFR, stable arterial hypertension and swellings. This degree of DN is characterized by sclerosis of 50-75% glomeruli.

AH stage was determined according to the order of the Ministry of Health of Ukraine № 384

dated 24.05.2012 «On Approval and Introduction of Medical-Technological Documents on Standard Medical Aid with Arterial Hypertension».

Doppler ultrasound of the renal parenchyma was made for all the patients including the control group to study renal circulation by means of the apparatus Logic 450.

The treatment was initiated according to the existing therapeutic principles of nephrological diseases found. Lisinopril in the dose of 10 mg twice a day was added to the standard treatment of patients suffering from stage 1 and 2 CKD with stage 2 AH during the whole period of examination and observation. The dose of Lisinopril was corrected individually depending on the response to antihypertensive therapy. Antihypertensive therapy was supplied by Furosemide 40 mg on an empty stomach and/or Amlodipine 5-10 mg/day as appropriate in individually selected doses.

The studies conducted were performed keeping to the Guidelines for Good Clinical Practice (GCP, 1996), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the World Medical Association (WMA) Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (1964-2000), and the order of the Ministry of Health of Ukraine №690 dated 23.09.2009, where a human being is an object of research. The study was approved by the Biomedical Ethics Committee of the Bukovinian State Medical University (experimental study; (Minutes No. 36 dated 17.11.2019) The article is recommended for publication by the Commission on Biomedical ethics in biomedical scientific research the Bukovinian State Medical University the protocol No. 4 dated 22 of April 2020. The state registration number is 0114U002471.

The data obtained were statistically processed by means of statistical programs ,,Excel5.0" with the calculation of mean value and standard deviation. Student's test was used to detect difference probability between the groups. Difference between the groups were considered to be reliable with the significance level $p < 0,05$. Mann- Whitney criterion was used for non-parametric calculations.

Results

Laboratory parameters of patients with diabetic nephropathy were analyzed before indication of angiotensin converting enzyme (ACE) inhibitors and calcium channel-blocking (CCB) agents. The most pronounced lipid imbalance was found in patients with DN and stage 2 AH which is indicative of considerable metabolic disorders in the organisms of patients. Correlations available were examined between the indices of blood lipid spectrum and the main kidney functions in the group of examined patients with CKD and stage 2 AH. Strong interrelations were found between daily proteinuria and parameters of low-density lipoproteins (LDL) ($r= 0,65$) ($p<0,05$), triglycerides ($r= 0,69$) ($p<0,05$) and general cholesterol ($r= 0,52$) ($p<0,05$), which is a direct mean force correlation. Strong reversible correlations were found between GFR and LDL parameters ($r= -0,71$) ($p<0,05$) and triglycerides ($r= -0,78$) ($p<0,05$). Therefore, reliable increase of LDL and triglycerides levels was indicative of CKD aggravation with AH available (Fig.1).

LDLs play a great role in creation of conditions to disturb renal microcirculation and further advance of CKD and stage 2AH.

Strong correlations of the main factors promoting aggravation of CKD (daily proteinuria, GFR) with the parameters of LDLs and triglycerides of blood, as well as LDLs and triglycerides with the major Doppler indices of the renal blood supply (Vs, Vd, RI, time-averaged maximal circulation rate (TAMCR)) confirm a great role of these lipid and especially non-invasive Doppler markers in detection of accelerated rates of CKD aggravation, which will enable to timely prevent the development of irreversible changes in the kidneys.

As far as activity of inflammatory process in the kidneys increases, permeability of the vascular capillary wall and small vessels increases, blood supply decreases, rheological blood properties deteriorate, which is of great importance for pathogenesis of chronic kidney disease, deteriorates permeability of the vascular wall and intensifies shifting of aggregation processes and inhibition of all the properties of red blood cells. With DM resulting in DN all the above processes increase to maximum. At the same time, activated free radical processes lead to disorders of morphofunctional properties of erythrocyte membranes, which might

promote disorders of microcirculatory processes in patients with chronic kidney disease. Arterial hypertension present in patients with CKD deteriorates blood supply in the small kidney vessels and decreases blood supply in them.

Morphofunctional properties of erythrocytes in patients suffering from stage 1 and 2 CKD and stage 2 AH were studied. Evaluation of the results of the study found the most pronounced decrease of erythrocyte deformability index (EDI) in patients with DN and AH ($p<0,05$). It should be noted that parameters were changed irrespective of availability or lack of AH, but practically in all the groups of the study the parameters of morphofunctional properties of erythrocytes differed reliably in the subgroups of patients. Thus, in patients without stage 2 AH the parameters of the relative viscosity of red blood cells (RBCs) suspension and peroxide erythrocyte hemolysis (PEH) were reliably lower than in patients with stage 2 AH respectively ($p<0,05$), and EDI was reliably lower in patients with AH than in the subgroup without stage 2 AH ($p<0,05$).

Correlations were investigated between the parameters of the morphofunctional properties of red blood cells and the main kidney functions in examined patients with CKD and stage 2 AH (Fig.2). The strongest correlations were found between the parameters of the main factors promoting CKD advance and relative viscosity of red blood cells (RBCs) suspension and peroxide erythrocyte hemolysis (PEH). Thus, strong correlations were found between GFR and relative viscosity of RBCs suspension ($r= -0,83$) ($p<0,05$) and PEH indices ($r= -0,79$) ($p<0,05$). Direct correlation of a mean force was found between GFR and EDI ($r= 0,48$) ($p<0,05$). Strong correlation was found between the quantitative index of daily proteinuria and PEH ($r= 0,89$) with ($p<0,05$), and mean force direct correlation between the quantitative index of daily proteinuria and relative viscosity of RBCs suspension ($r= 0,66$) ($p<0,05$). Reversible correlation of a mean force was found between the daily proteinuria parameter and EDI ($r= -0,49$) with ($p<0,05$).

Therefore, analysis of the whole changes in the morphofunctional properties of erythrocytes found that parameters of relative viscosity of RBCs suspension and PEH increase reliably with stage 1 and 2 CKD. They are mostly manifested in patients with DN event without stage 2 AH, but with AH changes become of an advancing character.

A part of 86 patients with AH during the whole period of the study used Amlodipine in the dose of 5 mg and Lisinopril in the dose of 10 mg once a day (42 patients) to normalize arterial pressure. The rest 46 patients received monotherapy with Lisinopril in the dose of 10 mg 1-2 times a day (individual doses) and diuretics as appropriate.

The treatment of patients with CKD was corrected according to the clinical recommendations issued by the State Institution «The Institute of Nephrology, the National Academy of Medical Sciences of Ukraine» (2012). Nephrological pathology was treated according to the existing principles of therapy of nephrological diseases found. Doppler ultrasound of the renal parenchymal vessels was made in order to control dynamics of changes of the renal blood supply. Tables 1.1 and 1.2 present the results of dynamic examination of the renal blood supply with underlying above treatment.

It should be noted that on the level of a. renales 6 months and a year later considerable changes were not found ($p>0,05$) under the action of both antihypertensive drugs in the group of patients with DN, who had a reliable decrease of the renal blood supply parameters on the primary examination. That is, the parameter neither deteriorated nor improved. On the level of a. segmentalis and a. interlobaris inconsiderable changes occurred demonstrated in Tables 1.1 and 1.2.

Table 1.1 shows that parameter of renal blood supply reliably decreased in many cases on the level of a. segmentalis after 6 months of treatment using antihypertensive therapy in the combination of Lisinopril and Amlodipine. In the group of patients with DN and AH the parameters were torpid and they did not respond to 6-month combined administration of Lisinopril in the dose of 10 mg and Amlodipine in the dose of 5 mg once a day.

Patients who received Lisinopril as a monotherapy of renal arterial hypertension did not show any reliable changes in the parameters of the renal blood supply after 6 months of treatment ($p>0,05$).

Table 1.2 shows the results of Doppler ultrasound after a year of treatment using

pathogenic antihypertensive therapy in the combination of Lisinopril in the dose of 10 mg and Amlodipine in the dose of 5 mg a day, and monotherapy with Lisinopril. Only parameters of the renal blood supply in patients with DN did not practically change (p>0,05).

In patients who received Lisinopril for a year practically all the parameters of the renal blood supply did not practically differ on both levels (a. segmentalis and a. interlobaris). The study confirms that patients with DN do not demonstrate reliable changes of Doppler parameters (p>0,05).

Thus, the majority of parameters of the renal blood supply after a combined administration of Lisinopril and Amlodipine for 6 months as a pathogenic treatment did not improve much in comparison with the beginning of treatment. Reliable improvement of the parameters of the renal blood supply was registered after a combined administration of Lisinopril and Amlodipine for 12 months, inconsiderable improvement of blood supply in the small renal vessels occurred which provided slowing down of CKD aggravation. In respect of the above mentioned examined correlations of Doppler parameters and the main factors of CKD aggravation (GFR, daily proteinuria) and the main biochemical markers of CKD advance, a combined administration of Lisinopril and Amlodipine should be preferred.

Thus, analysis of examination of patients with stage 1 and 2 CKD and stage 2 AH showed a great value of Doppler parameters in order to determine prognosis of CKD aggravation in patients with DN and stage 2 AH. In our opinion, performing color duplex Doppler ultrasound of the renal circulation is of great importance in timely diagnostics and dynamic control of the quality of treatment of patients with chronic kidney disease and arterial hypertension, which will provide timely introduction of therapeutic-preventive measures in order to slow down aggravation of chronic kidney disease and development of terminal stage of the disease resulting in treatment by means of hemodialysis.

Discussion

During the use of nephroprotective therapy the interrelations between the parameters of renal blood supply and proteinuria level in the examined patients were evaluated. Since, patients with proteinuria level till 2 g/day were involved into the study, the interrelations found were estimated. Thus, in patients with absent proteinuria in daily urine the parameters of TAMCR and RI practically did not differ from the norm. Patients with the parameter of daily proteinuria lower than 1g/day presented the parameter of an average by time maximal blood supply differed reliably (0,17±0,01 m/sec) against (0,20±0,01 m/sec) in patients without proteinuria in daily urine (p<0,05), and RI of these patients did not differ (p>0,05). In patients with daily proteinuria more than 1 g/day the examined parameters of the renal blood supply differed reliably. Thus, TAMCR was reliably lower (0,14±0,02 m/sec) against (0,20±0,01 m/sec) (p<0,05), and RI was reliably higher respectively (0,74±0,02) against (0,54±0,03) with (p<0,05).

Identification of the parameters of the renal blood supply plays an important role in non-invasive prognosis of an aggravating course of CKD, especially with arterial hypertension available[26,27].

Nowadays there is no sufficient evidence concerning prognostic value of the chosen markers of free radical oxidation (FRO) with kidney lesions under conditions of CKD course, diabetic nephropathy with arterial hypertension II degree, and the character of damages of the kidney structures with the above pathology is not described [28,29,30].

Imbalance in the lipid free radical oxidation (LFRO) system plays an important role in disturbances of the renal blood supply and creates conditions for increased resistance of the renal vessels. Increased LFRO intensity in patients with stage 1 and 2 CKD and stage 2 AH is of great importance in aggravation of pathological disorders in the renal circulation system. The most substantial decompensation of LFRO processes occurred in patients with stage 2 CKD (diabetic nephropathy) with stage 2 AH available.

Dyslipidemia is one of the important risk factors in aggravation of chronic kidney disease, especially with AH available [31,32]. Our research examined peculiarities of lipid imbalance in the blood of patients with stage 1 and 2 CKD and stage 2 AH. The parameters of lipid blood spectrum in

patients with stage 1 and 2 CKD, and stage 2 AH were characterized.

Analysis of the data obtained found that lipid metabolism parameters differed most considerably from the norm in patients with DN and AH, which was reliably different from the appropriate parameters in the group of patients suffering from DN without AH ($p<0,05$). It should be noted, that in patients suffering from DN without AH the parameters of lipid spectrum undergo considerable changes in comparison with normal findings in the group of healthy individuals and all the rest of the patients without stage 2 AH. The most pronounced lipid imbalance was found in patients with DN and stage 2 AH, which is indicative of considerable metabolic disorders in the organism of patients reflected in renal function. The level of triglycerides in the blood mostly influences on the time of a time-averaged maximal circulation rate and therefore, to our mind, this is the parameter that should be paid special attention to in identification of lipid markers influencing on acceleration of CKD aggravation with AH. Thus, LDL and triglycerides of the blood can be markers indicative of disorders of the renal blood supply in the small renal vessels further promoting quick aggravation of CKD with AH.

As far as activity of inflammatory process in the kidneys increases, the permeability of the vascular capillary wall and small renal vessels increases as well. Blood supply slows down, rheological blood properties deteriorate, which is of great value in pathogenesis of chronic kidney disease, especially with immune inflammation, which deteriorates permeability of the vascular wall and intensifies disorders of aggregation processes and inhibits all the properties of red blood cells. With diabetes mellitus and diabetic nephropathy resulted from it all the above processes increase to maximum, since with underlying inhibited immunity and considerable disorders of metabolic processes in the organism of patients, disturbances of the renal blood flow increase much more. CKD and arterial hypertension in patients deteriorates blood supply in the small renal vessels and decreases blood flow in them. Therefore, today the problems occurring from the side of morphofunctional state of erythrocytes in such patients remain uncertain, as well as interrelations of these changes with Doppler parameters of the renal blood supply.

Condition of patients suffering from stage 1 and 2 CKD with DN is associated with pronounced disorders of the morphofunctional properties of red blood cells. In patients with AH these disorders intensify more, which is mostly manifested in the group of patients with DN and stage 2 AH. It is indicative of an important role of disturbances of these mechanisms for microcirculatory disorders in this group of patients.

Improvement of efficacy of treatment of patients with CKD and AH is one of the urgent issues of current nephrology, which is caused by high sickness rate of CKD and increase of a part of patients with renoparenchymal arterial hypertension associated with complications and aggravation of CKD resulting in disorders of functional ability of the kidneys, disability of such patients and impossibility of their life without regular sessions of detox programs, and of course, considerable deterioration of the quality and life span of patients[33]. All the patients in our research received hypotensive mono- and combined therapy depending on the stages of AH and CKD.

Considering the results of our research and numerous interrelations of Doppler parameters of the renal blood supply found on the level of small vessels of the kidneys, and a.interlobaris in partikular, with the main factors promoting CKD aggravation (GFR and daily proteinuria), as well as with biochemical markers playing a great role in CKD aggravation, it should be reasonable to our mind to analyze the dynamics of Doppler ultrasound changes in the renal blood supply during a remote period of time, that is, 6 months and one year since the primary examination of patients.

It should be noted that considerable changes were not found ($p>0,05$) at the level of a. renales in 6 months and in a year under the action of both antihypertensive drugs in the group of patients suffering from DN who presented reliable decrease of the renal blood supply parameters at the primary examination. That is, these parameters neither deteriorated nor increased.

Changes occurred at the levels of a. segmentalis and a. interlobaris. The parameters of the renal blood supply after 6 months of treatment using combination of Lisinopril and Amlodipine as antihypertensive pathogenic therapy changed

reliably in many cases at the level of a. segmentalis. In patients suffering from DN and AH the parameters were torpid and did not respond to the 6-month combined therapy with Lisinopril and Amlodipine. Results of Doppler ultrasound in a year since the use of pathogenic antihypertensive therapy in the form of a combined administration of Lisinopril in the dose of 10 mg and Amlodipine in the dose of 5 mg a day did not find any considerable changes. The parameters of the renal blood flow in patients with DN did not change practically (p>0,05).

Thus, combined administration of Lisinopril and Amlodipine as pathogenic therapy do not considerably change the renal blood supply parameters for the better in patients with DN during 6 and 12-month period, but the disease does not aggravate with gradual decrease of GFR and development of terminal stage of renal failure.

In our opinion, color duplex Doppler ultrasound of the renal blood supply will be of great importance in timely diagnostics and during dynamic control over the quality of treatment of patients suffering from chronic kidney disease with arterial hypertension, providing timely initiation of therapeutic-preventive measures in order to slow down aggravation of chronic kidney disease.

References

1. Kimmel P. L., Rosenberg M. E. Introduction: chronic renal disease. Chronic renal disease / ed. by P. L. Kimmel, M. E. Rosenberg. 2nd ed. London : Academic Press, 2020. P. 3–6.
2. 2. Zhou Y., Yang J. Chronic kidney disease: overview. Chronic kidney disease: diagnosis and treatment / ed. by J. Yang, W. He. Singapore : Springer, 2020. P. 3–12.
3. 3. Grams M. E., Levey S. A., Coresh J. Epidemiology of kidney disease. Brenner and Rector's the kidney / ed. by A. S. L. Yu et al. 11th ed. Philadelphia : Elsevier, 2020. P. 616–639.
4. Agarwal A., Nath K. A. Pathophysiology of chronic kidney disease progression: organ and cellular considerations. Chronic renal disease / ed. by P. L. Kimmel, M. E. Rosenberg. 2nd ed. London : Academic Press, 2020. P. 263–278.
5. Parikh S. V., Haddad N. J., Hebert L. A. Retarding progression of kidney disease. Comprehensive clinical nephrology / ed. by J. Feehally et al. 6th ed. Philadel- 367 phia : Elsevier, 2019. P. 924–934.
6. Bjornstad P., Lytvyn Y., de Zeeuw D., Cherney D. Pathogenesis, pathophysiology, and treatment of diabetic nephropathy. National Kidney Foundation primer on kidney diseases / ed. by S. J. Gilbert et al. 7th ed. Philadelphia : Elsevier, 2018. P. 252–265.
7. Epidemiology of diabetic kidney disease. Brenner and Rector's the kidney / A. Fornoni et al. ; ed. by A. S. L. Yu et al. 11th ed. Philadelphia : Elsevier, 2020. P. 1327–1379.
8. Benigni A., Perico N., Remuzzi G. Pathophysiology of disease progression in proteinuric and nonproteinuric kidney disease. Comprehensive clinical nephrology / ed. by J. Feehally et al. 6th ed. Philadelphia : Elsevier, 2019. P. 913–923.
9. Taal M. W. Classification and management of chronic kidney disease. Brenner and Rector's the kidney / ed. by A. S. L. Yu et al. 11th ed. Philadelphia : Elsevier, 2020. P. 1946–1976.
10. Gliga M, Cozma C, Gliga M, Georgescu R, Tilinca M. Doppler ultrasound of kidney interlobar arteries in different nephropaties. *Ultraschall in der Medizin / European Journal of Ultrasound* 2008; 29:S1.
11. Lee S, Oh H, Lee E, et al. Blood pressure control during chronic kidney disease progression. *American Journal of Hypertension* 2017; 30: 610-616.
12. Boddi M. Renal ultrasound (and Doppler sonography) in hypertension: an update. *Advances in Experimental Medicine and Biology* 2016: 191-208.
13. Jahangiry L, Ghanbari J, Abbasalizad Farhangi M, Sarbakhsh P, Ponnet K. Predictors of poor blood pressure control among Iranian hypertensive patients. BMC Res Notes. 2017 Dec 4;10(1):668. doi: 10.1186/s13104-017-2971-4.PMID: 29202794
14. Lepeytre F, Cardinal H, Fradette L, Verhave J, Dorais M, LeLorier J, Pichette V, Madore F. The impact of renal protection clinics on prescription of and adherence to cardioprotective drug therapy in chronic kidney disease patients. Clin Kidney J. 2017 Jun;10(3):375-380. doi:

10.1093/ckj/sfw144. Epub 2017 Feb 18.PMID: 28616215
15. Parker SC, Hannah A, Brooks M, Louis WJ, O'Callaghan. Renal artery stenosis: a disease worth pursuing. CJ.Med J Aust. 2001 Aug 6;175(3):149-53.PMID: 11548082
16. Tedla FM, Brar A, Browne R, Brown C. Hypertension in chronic kidney disease: navigating the evidence. *International Journal of Hypertension* 2011; 132405.
17. Parati G, Castiglioni P, Omboni S, Faini A, Parati G., Castiglioni P, Omboni S, Faini A. Effects on 24-hour blood pressure variability of ace-inhibition and calcium channel blockade as monotherapy or in combination. Sci Rep. 2018 Sep 13;8(1):13779. doi: 10.1038/s41598-018-31746-2.PMID: 30213981
18. Robinson TG, Davison WJ, Rothwell PM, Potter JF.Randomised controlled trial ofa Calcium Channel or Angiotensin Converting Enzy me Inhibitor/Angiotensin Receptor Blocker Regime to Reduce Blood Pressure Variability following Ischaemic Stroke (CAARBS): a protocol for a feasibility study.
19. Segura J, Ruilope L. Hypertension in moderate-to-severe nondiabetic CKD patients. *Advances in Chronic Kidney Disease* 2011;18: 23-
20. Sun J, Xie J, Kang L, Ferro A, Dong L, Xu B. Amlodipine Ameliorates Ischemia-Induced Neovascularization in Diabetic Rats through Endothelial Progenitor Cell Mobilization. Biomed Res Int. 2016;2016:3182764. doi: 10.1155/2016/3182764. Epub 2016 May 8.PMID: 27243031
21. Karasavvidou D, Boutouyrie P, Kalaitzidis R, Kettab H, Pappas K, Stagikas D, Antonakis N, Tsalikakis D, Elisaf M, Laurent S. Arterial damage and cognitive decline in chronic kidney disease patients. J Clin Hypertens (Greenwich). 2018 Sep;20(9):1276-1284. doi: 10.1111/jch.13350. Epub 2018 Jul 14.PMID: 30006952
22. Rutkowski B., Tylicki L. Nephroprotective action of renin-angiotensin-aldosterone system blockade in chronic kidney disease patients: the landscape after ALTITUDE and VA NEPHRON-D trails. Journal of renal nutrition. 2015. Vol. 25 (2). P. 194–200.
23. Mussa BM, Hamoudi RA, Abusnana SE. Association Trends Between Antihypertensive Drug Therapies and Diastolic Hypotension in Emirati Patients with Type 2 Diabetes: A Single-Center Retrospective Longitudinal Study. Diabetes Ther. 2018 Oct;9(5):1853-1868. doi: 10.1007/s13300-018-0469-2. Epub 2018 Jul 24.PMID: 30043211
24. Ojrzanowski M, Kasprzak JD, Peruga JZ, Kurpesa M, Jankowski Ł, Sahni S. Resistant hypertension: Renal denervation or pharmacovigilance? Insights from a renal denervation screening program. M.Adv Clin Exp Med. 2019 Nov;28(11):1525-1530. doi: 10.17219/acem/104550.PMID: 31693316
25. Hong D, Shi W, Lu X, Lou Y, Li L. Development and Validation of a Medication Selection Model Under Clinical Application of Renin-Angiotensin Inhibitor Combined with Calcium Channel Blocker for Hypertension Patients. Med Sci Monit. 2020 Apr 14;26:e923696. doi: 10.12659/MSM.923696.PMID: 32285846
26. Handler J. Cleve .Clinical challenges in diagnosing and managing adult hypertension.Clin J Med. 2015 Dec;82(12 Suppl 2):S36-41. doi: 10.3949/ccjm.82.s2.06.PMID: 26694890
27. Jahangiry L, Ghanbari J, Abbasalizad Farhangi M, Sarbakhsh P, Ponnet K. Predictors of poor blood pressure control among Iranian hypertensive patients. BMC Res Notes. 2017 Dec 4;10(1):668. doi: 10.1186/s13104-017-2971-4.PMID: 29202794
28. Jarari N, Rao N, Peela JR, Ellafi KA, Shakila S, Said AR, Nelapalli NK, Min Y, Tun KD, Jamallulail SI, Rawal AK, Ramanujam R, Yedla RN, Kandregula DK, Argi A, Peela LT.A review on prescribing patterns of antihypertensive drugs. Clin Hypertens. 2016 Mar 27;22:7. doi: 10.1186/s40885-016-0042-0. eCollection 2015.PMID: 27019747
29. Walther CP, Chandra A, Navaneethan S. Blood pressure parameters and morbid and mortal outcomes in nondialysis-dependent chronic kidney disease..Curr Opin Nephrol Hypertens. 2018 Jan;27(1):16-22.doi:10.1097/MNH.0000000000000375.PMID: 29045334

30. Allon M, Litovsky SH, Tey JCS, Sundberg CA, Zhang Y, Chen Z, Fang Y, Cheung AK, Shiu YT. Abnormalities of vascular histology and collagen fiber configuration in patients with advanced chronic kidney disease. J.Vasc Access. 2019 Jan;20(1):31-40. doi: 10.1177/1129729818773305. Epub 2018 May 9.PMID: 29742957
31. Botdorf J, Chaudhary K, Whaley-Connell A. Hypertension in cardiovascular and kidney disease. *Cardio Renal Medicine* 2011; 1: 183-192.
32. Novychenko S, Zub L, Kovalenko S, Influence of angiotensin converting ensim inhibitors and calcium channel blockers on the blood circulation in the kidney parenchyma. PhOL. 2020, N2, p. 251-261.
33. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International* 2013;3: 1-150.

Table 1.1. Quantitative characteristics of blood supply in the renal vessels 6 months after treatment (n, M±m)

Levels of examination	Doppler parameters	Individuals examined	
		Practically healthy	DN with arterial hypertension
Lisinopril + Amlodipine			
a. segmentalis	Vs (cm/sec) Vd (cm/sec) TAMCR (m/sec) Vvol (ml/min) IR	56,38 ± 3,32 24,22± 2,28 0,29± 0,06 98,71 ± 2,35 0,55 ± 0,05	43,01 ± 2,11* 14,95± 2,17* 0,19± 0,03* 88,22 ± 2,34* 0,63 ± 0,04*
a.interlobaris	Vs (cm/sec) Vd (cm/sec) TAMCR (m/sec) Vvol (ml/min) IR	34,87 ± 2,12 17,42± 2,26 0,21± 0,06 91,35 ± 2,39 0,54 ± 0,02	23,51 ± 2,12* 9,12± 2,14* 0,13± 0,06* 81,44 ± 2,12* 0,72 ± 0,03*
Lisinopril			
a. segmentalis	Vs (cm/sec) Vd (cm/sec) TAMCR (m/sec) Vvol (ml/min) RI	56,38 ± 3,32 24,22± 2,28 0,29± 0,06 98,71 ± 2,35 0,55 ± 0,05	42,10 ± 2,11* 14,56± 2,34* 0,23± 0,03* 88,92 ± 2,44* 0,74 ± 0,05*
a.interlobaris	Vs (cm/sec) Vd (cm/sec TAMCR (m/sec) Vvol (ml/min) RI	34,87 ± 2,12 17,42± 2,26 0,21± 0,06 91,35 ± 2,39 0,54 ± 0,02	22,55 ± 2,16* 8,83± 2,32* 0,14± 0,06* 80,55 ± 2,16* 0,72 ± 0,02*
Notes: * - p<0,05 in comparison with the group of healthy individuals; ˆ - p<0,05 in comparison with DN patients			

Tab.1.2 Quantitative characteristics of blood supply in the renal vessels 12 months after treatment (n, M±m)

Levels of examination	Doppler parameters	Individuals examined	
		Practically healthy	DN with arterial hypertension
Lisinopril + Amlodipine			
a. segmentalis	Vs (cm/sec) Vd (cm/sec TAMCR (m/sec) Vvol (ml/min) RI	56,38 ± 3,32 24,22± 2,28 0,29± 0,06 98,71 ± 2,35 0,55 ± 0,05	43,92 ± 2,15* 14,99± 2,27* 0,19± 0,04* 88,79 ± 2,13* 0,63 ± 0,05*
a.interlobaris	Vs (cm/sec) Vd (cm/sec TAMCR (m/sec) Vvol (ml/min) RI	34,87 ± 2,12 17,42± 2,26 0,21± 0,06 91,35 ± 2,39 0,54 ± 0,02	22,53 ± 2,42* 9,33± 2,24* 0,14± 0,05* 82,04 ± 2,44* 0,70 ± 0,02*
Lisinopril			
a. segmentalis	Vs (cm/sec) Vd (cm/sec TAMCR (m/sec) Vvol (ml/min) RI	56,38 ± 3,32 24,22± 2,28 0,29± 0,06 98,71 ± 2,35 0,55 ± 0,05	42,66 ± 2,38* 14,89± 2,77* 0,23± 0,04* 89,11 ± 2,04* 0,72 ± 0,04*
a.interlobaris	Vs (cm/sec) Vd (cm/sec TAMCR (m/sec) Vvol (ml/min) RI	34,87 ± 2,12 17,42± 2,26 0,21± 0,06 91,35 ± 2,39 0,54 ± 0,02	23,35 ± 2,18* 9,13± 2,44* 0,14± 0,05* 81,62 ± 2,11* 0,70 ± 0,01*

Notes: * - p<0,05 in comparison with the group of healthy individuals;
ˆ - p<0,05 in comparison with DN patients

Figure 1. Correlations between blood lipid level and main kidney functions.

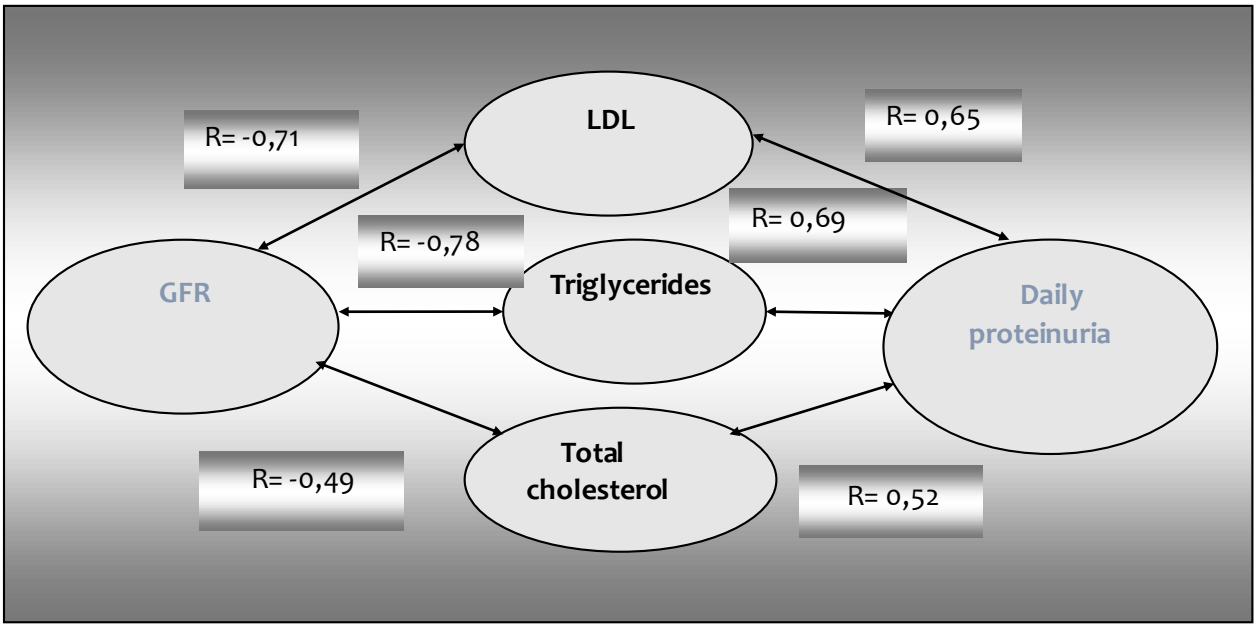

Figure 2. Correlations between the parameters of the morphofunctional properties of red blood cells and the main kidney functions