DOI: 10.20514/2226-6704-2024-14-1-30-37
УДК [616.61-002-06:616.12-008.331.1]:616.136.7
EDN: DRTGUW

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ФАКТОРЫ РИСКА СТРУКТУРНОЙ ПЕРЕСТРОЙКИ МИКРОЦИРКУЛЯТОРНОГО РУСЛА ПОЧЕК У ПАЦИЕНТОВ С ГЛОМЕРУЛОНЕФРИТОМ И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Factor Analysis for Predicting the Structural Reorganization of the Microvasculature of the Kidneys in Patients with Glomerulonephritis and Arterial Hypertension

Резюме

Цель. Оценка взаимосвязи клинико-лабораторных и морфологических факторов с ремоделированием артерий почек малого диаметра у пациентов с гломерулонефритом (ГН) и артериальной гипертензией (АГ). **Материалы и методы.** В исследование включено 105 пациентов (средний возраст 37,1±1,2 лет) с первичным ГН и АГ, показаниями к выполнению нефробиопсии. Всем пациентам проведено стандартное нефрологическому профилю обследование, морфологическое исследование нефробиоптата с оценкой изменений почечной ткани с описанием изменений, происходящих при наличии гломерулонефрита, соответствующее индивидуальной выраженности патологического процесса. Оценивалось наличие признаков тубулоинтерстициального компонента повреждения (или тубулоинтерстициальный компонент — ТИК) в виде тубулоинтерстициального воспаления (ТИВ), фиброза (ТИФ). Выполнена вазометрия междольковой артерии (МА). Признаком ремоделирования МА было принято считать величину комплекса интима-медиа (КИМ) более 30,43 мкм. **Результаты.** Среди клинико-лабораторных факторов риска статистически значимое влияние на вероятность увеличения КИМ имеют повышение уровня систолического артериального давления

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(χ^2-критерий = 5,76, p = 0,016), стадии АГ (χ^2-критерий = 9,45, p = 0,002), уровня мочевины крови (χ^2-критерий = 8,11, p = 0,004), уменьшение скорости клубочковой фильтрации (χ^2-критерий = 5,0, p = 0,025), увеличение стадии хронической болезни почек (χ^2-критерий = 10,32, p = 0,001). Наличие признаков прогрессирования ГН, таких как повышение скорости оседания эритроцитов (СОЭ) или белка в моче, статистически значимого влияния на риск ремоделирования МА не установило (p>0,05). На вероятность увеличения КИМ МА влияют наличие гиалиноза капиллярных петель клубочка (χ^2-критерий = 7,56, p = 0,006), перигломерулярного гиалиноза (χ^2-критерий = 6,96, p = 0,008), склероза клубочка (χ^2-критерий = 3,9, p = 0,048), увеличение фиброза тубулоинтерстиция (χ^2-критерий = 12,16, p = 0,0005). **Заключение.** При ГН и АГ ремоделирование сосудов почек малого диаметра происходит из-за влияния АГ и ее выраженности, тубулоинтерстициальных изменений почечной ткани. Получены новые факторы риска сосудистого ремоделирования –гломерулопатии, которые проявляются в склерозе клубочка, перигломерулярном гиалинозе и гиалинозе капиллярных петель клубочка. В то же время, воспалительные и аутоиммунные механизмы ГН не влияют на изменение сосудистой стенки. Роль АГ является определяющей в изменении структуры почек малого диаметра.

Ключевые слова: *гломерулонефрит, артериальная гипертензия, ремоделирование артерий малого диаметра, междольковая артерия*

Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 01.06.2023 г.
Принята к публикации 17.01.2024 г.

Для цитирования: Левицкая Е.С., Батюшин М.М., Синельник Е.А. и др. ФАКТОРЫ РИСКА СТРУКТУРНОЙ ПЕРЕСТРОЙКИ МИКРОЦИРКУЛЯТОРНОГО РУСЛА ПОЧЕК У ПАЦИЕНТОВ С ГЛОМЕРУЛОНЕФРИТОМ И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ. Архивъ внутренней медицины. 2024; 14(1): 30-37. DOI: 10.20514/2226-6704-2024-14-1-30-37. EDN: DRTGUW

Abstract
Objectives. Evaluation of the relationship of clinical, laboratory and morphological factors with remodeling of small-diameter renal arteries in patients with glomerulonephritis (GN) and arterial hypertension (AH). **Materials and methods.** The study included 105 patients (average age 37.1±1.2 years) with primary GN and hypertension who had indications for morphological investigation of kidney tissue. All patients underwent a standard examination for kidney disease, a morphological study of kidney tissue with a description of the changes that occur in the presence of glomerulonephritis, corresponding to the individual severity of the pathological process. The presence of signs of a tubulointerstitial component of damage (or tubulointerstitial component — TIC) in the form of tubulointerstitial inflammation (TIV), fibrosis (TIF) was assessed. Vasometry of the interlobular artery (IA) was performed. The value of the intima-media complex (IMC) was considered to be a sign of IA remodeling. A sign of MA remodeling was considered to be an intima-media complex (IMC) value of more than 30.43 μm. **Results.** Among clinical and laboratory risk factors, an increase in systolic blood pressure has a statistically significant effect on the likelihood of increasing IMC (χ2-criterion = 5.76, p = 0.016), arterial hypertension stage (χ2-criterion = 9.45, p = 0.002), blood urea level (χ2-criterion = 8.11, p = 0.004), decrease in glomerular filtration rate (χ2-criterion = 5.0, p = 0.025), increase in the stage of chronic kidney disease (χ2-criterion = 10.32, p = 0.001). The presence of signs of GN progression, such as an increase in erythrocyte sedimentation rate (ESR) or proteinuria, did not have a statistically significant effect on the risk of IA remodeling (p>0.05). The increase in IA IMC is affected by the presence of hyalinosis of glomerular capillary loops (χ2-criterion = 7.56, p = 0.006), periglomerular hyalinosis (χ2-criterion = 6.96, p = 0.008), sclerosis of the glomerulus (χ2-criterion = 3.9, p = 0.048), increased fibrosis of tubulointerstitium (χ2-criterion = 12.16, p = 0.0005). **Conclusion.** In GN and AH, remodeling of small-diameter renal vessels occurs due to the influence of AH and its severity, tubulointerstitial changes in the renal tissue. New risk factors for vascular remodeling have been obtained — changes in the glomerulus. At the same time, the inflammatory and autoimmune mechanisms of GN were not associated with changes in the vascular wall. The role of hypertension is decisive in changing the structure of small-diameter kidneys.

Key words: *glomerulonephritis, arterial hypertension, remodeling of small diameter arteries, interlobular artery*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 01.06.2023
Accepted for publication on 17.01.2024

For citation: Levitskaya E.S., Batiushin M.M., Sinel'nik E.A. et al. Factor Analysis for Predicting the Structural Reorganization of the Microvasculature of the Kidneys in Patients with Glomerulonephritis and Arterial Hypertension. The Russian Archives of Internal Medicine. 2024; 14(1): 30-37. DOI: 10.20514/2226-6704-2024-14-1-30-37. EDN: DRTGUW

AH — arterial hypertension, BP — blood pressure, GN — glomerular nephritis, DBP — diastolic blood pressure, IMC — intima-media complex, IA — interlobular artery, SUP — spot urine protein, SBP — systolic blood pressure, eGFR — estimated glomerular filtration rate, DUP — daily urine protein, TII — tubulointerstitial inflammation, TIC — tubulointerstitial component, TIF — tubulointerstitial fibrosis, CKD — chronic kidney disease

Introduction

Kidney vascular supply has a unique anatomical and functional organisation [1], which determines the vital physiological functions of the organ with adequate blood supply, formation and regulation of the perfusion pressure. Vascular structural or functional remodelling is associated with impaired organ trophism and organ failure development. It is worth noting that the condition of the arterial bed should be monitored not only at the main artery level, but also in the microcirculation. General damage to small arteries and arterioles can result in irreversible remodelling of main arteries and kidney dysfunction.

Glomerular nephritis (GN) is a socially significant disease [2, 3]. The natural course of GN results in chronic kidney disease, associated diseases and conditions (arterial hypertension, anaemia, thrombosis, etc.), high risk of death and permanent disability. It is well known that the pathogenic mechanism behind GN is intraglomerular immune inflammation, that leads to glomerular and tubulointerstitial damage [4]. However, morphological examination shows not only damage to glomerulus cells, but also structural changes in small arteries in the kidney. The nature of vascular remodelling in arteries and arterioles in GN is still not completely clear [5]. There are key conditions that cause structural remodelling in the microcirculation in patients with GN. "Vascular exhaustion" is a phenomenon that underlies the basic theory of changes in small arteries in response to tissue rearrangements in the dependent organ. This process can be seen in the pathophysiological mechanism "function, then form", i.e. the vascular bed changes in response to a larger demand by structurally modified renal tissue. Another condition for remodelling of small arteries is high blood pressure (BP) which is a common clinical manifestation of GN. Also, there can be the effect of endotheliotropic factors, a higher level of which is observed in cytokine inflammation in response to an autoimmune process, oxidative stress, effect of toxic metabolites in GN.

The objective of our study was to assess the association between clinical, laboratory and morphological factors and remodelling of small renal arteries in patients with GN and AH.

Materials and Methods

The study enrolled 105 patients with GN and AH, of which 62 were men and 43 were women. The mean GN duration was 4.13 [0.04; 20.0] years. The age of patients was 37.1 ± 1.2 years. Clinical study design is presented in Figure 1.

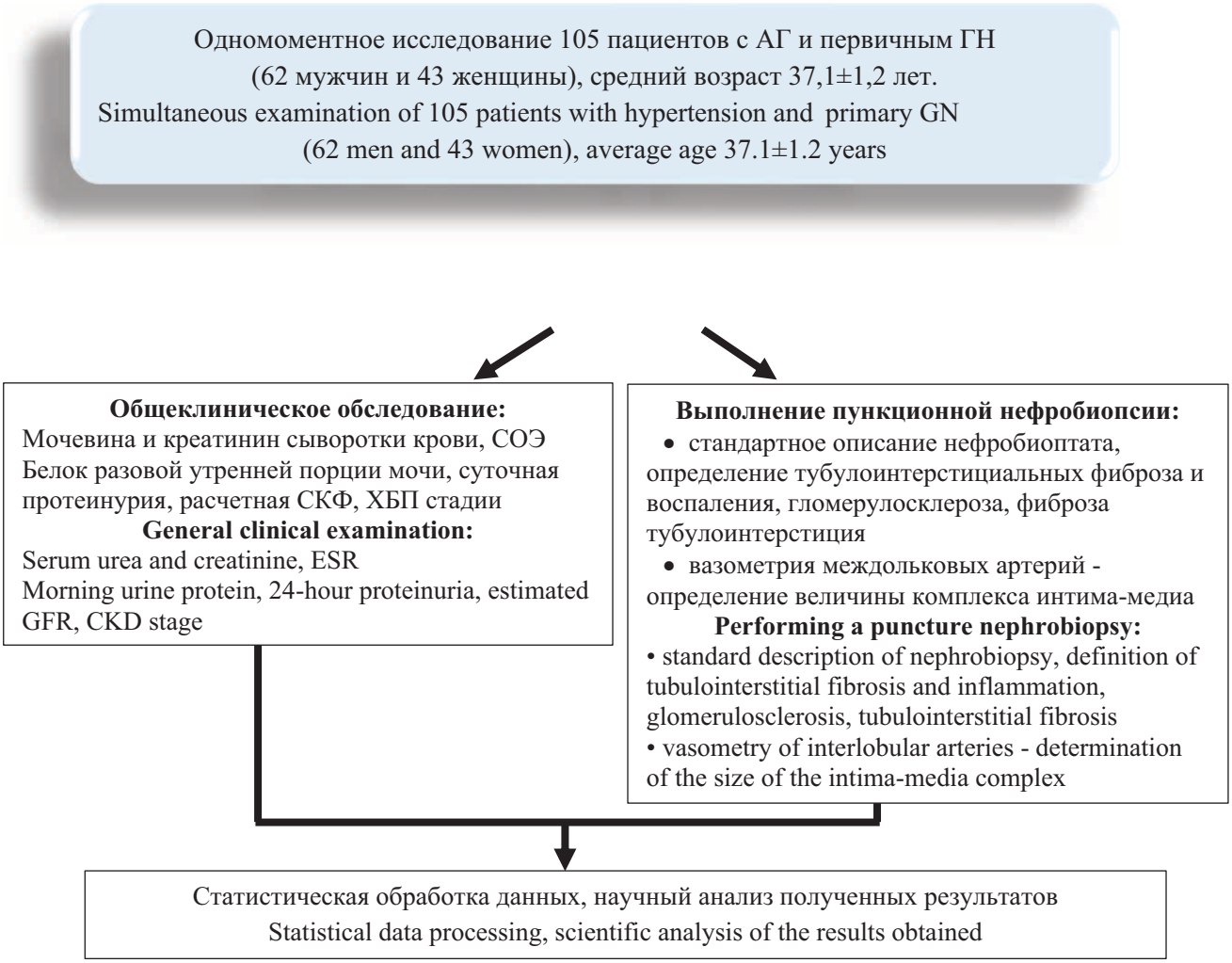

Figure 1. *Clinical study design*
Note: AH — arterial hypertension, GN — glomerulonephritis, ESR — erythrocyte sedimentation rate, GFR — glomerular filtration rate, CKD — chronic kidney disease

The inclusion criterion in this study was arterial hypertension and indication for needle renal biopsy (observation of any pathologic urine sediment in patients with GN (spot urine protein concentration over 0.033 g/L and over 150 g/day, erythrocyturia of over 3/HPF), stage 1–4 CKD). Exclusion criteria were secondary GN, inflammations of any origin, decompensated comorbidities.

All patients underwent a medical examination. Laboratory tests measured urea, serum creatinine, erythrocyte sedimentation rate (ESR), spot urine protein (SUP) and daily urine protein (DUP). Glomerular filtration rate (GFR) was calculated using the formula developed by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) [6]. Estimated GFR was used to determine the stage of chronic kidney disease (CKD) (KDIGO, 2012) [7]. Each CKD stage was graded. Grade 1 corresponded to stage 1 CKD, grade 2 — to stage 2 CKD, grade 3 — to stage 3a CKD, grade 4 — to stage 3b CKD, grade 5 — to stage 4 CKD. AH severity and stage were recorded; systolic (SBP) and diastolic (DBP) blood pressure were recorded during the first encounter with the patient; the highest SBP and DBP from the medical record were recorded as well. Clinical characteristics of study subjects are presented in Table 1.

At the time of enrolment, out of 105 patients, 75 patients had uncontrolled AH, BP in 17 patients corresponded to grade 1, in 44 patients — to grade 2, and in 14 patients — grade 3. 20 patients were diagnosed with stage III AH, 59 patients had stage II AH, and the rest were diagnosed with stage I AH. At the time of enrolment, all patients were taking antihypertensive medications.

All patients underwent needle renal biopsy and measurement of small renal vessels. Measurements of vessel diameter were performed using Leica DMD108 microscope (Leica Microsystems, Germany). Inner and outer diameter, thickness of vessel intima and media were measured. The intima-media complex (IMC) value was obtained by adding the values for intima and media. Of note, microtome sections of renal bioptate created various combinations of arteries (transverse, longitudinal). In order to establish the true diameter of a small renal artery, the rules of vascular geometry were used, and the smallest diameter was used as a true value.

Renal bioptate examination included standard description of changes in GN, which corresponded to the individual intensity of the pathological process. The presence of the signs of tubulointerstitial component of the damage (or tubulointerstitial component (TIC)) in the form of tubulointerstitial inflammation (TII), fibrosis (TIF) were evaluated. Table 2 shows the key results of renal biopsy in patients enrolled in the study.

Given that interlobular artery (IA) was the most common observation in renal bioptate analysis, it was decided to record remodelling results for IA only in order to ensure statistical homogeneity of the test data. IA IMC was recorded as a factor characterising the structural remodelling of IA. Mean IA IMC was 32.26 ± 1.34 μm. The study evaluated grade values of IA IMC based on the median value of 30.43 μm. IA IMC of less than 30.43 μm corresponded to grade 0, while a value of 30.43 μm or over — to grade 1.

Table 1. *Clinical and laboratory data of patients with glomerulonephritis and hypertension*

Criterion	Average value
SBP, mm Hg, Me [IQR]	128 [100; 200]
DBP, mm Hg, Me [IQR]	82,4 [60; 120]
SBP max, mm Hg, Me [IQR]	152,7 [90; 240]
DBP max, mm Hg, Me [IQR]	93,7 [60; 130]
Creatinine, μmol/l, Me [IQR]	104,0 [30,0; 232,7]
Urea, mmol/l, Me [IQR]	8,0 [1,8; 38,9]
eGFR, ml/min/1.73m^2, M+SD	87,1±3,9
CKD stage 1, abs (%)	52 (49,52)
CKD stage 2, abs (%)	31 (29,52)
CKD stage 3A, abs (%)	9 (8,57)
CKD stage 3B, abs (%)	9 (8,57)
CKD stage 4, abs (%)	4 (3,82)
ESR, mm/h, M+SD	24,6±18,6
Protein concentration in urine sample, g/l, Me [IQR]	2,8 [0; 32,0]
24h proteinuria, g/l, Me [IQR]	3,8 [0; 26,4]

Note: SBP — systolic blood pressure, DBP — diastolic blood pressure, SBP $_{max}$ — maximum values of the patient's SBP, DBP $_{max}$ — maximum values of the patient's DBP, eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease, ESR — erythrocyte sedimentation rate

Table 2. *Characterization of morphological changes in the nephrobioptate of patients with glomerulonephritis and hypertension*

Sign *	Prevalence, abs (%)
Mesangium expansion	77 (73,3)
Sclerosis of the mesangium	33 (31,4)
Glomerulus enlargement	41 (39,1)
Segmental sclerosis of capillary loops of the glomerulus	63 (60,0)
Segmental hyalinosis of capillary loops of the glomerulus	26 (24,8)
Fusion of capillary loops	89 (84,8)
Obliteration of capillary loops	6 (5,7)
Mesangial hypercellularity	62 (59,1)
Endothelial hypercellularity	9 (8,6)
Periglomerular focal fibrosis	77 (73,3)
Periglomerular focal hyalinosis	21 (20,0)
Glomerular hyalinosis	54 (51,4)
Glomerular fibrosis	41 (39,1)
Tubulointerstitial inflammation	64 (60,9)
Tubulointerstitial fibrosis	79 (75,2)
Tubulointerstitial component	86 (81,9)

Note: * — presence of a sign in the study cohort of patients

The study was conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee at the Federal State Budgetary Educational Institution of Higher Education Rostov State Medical University of the Ministry of Health of Russia. Before inclusion in the study, study subjects signed the informed consent form.

Statistical data analysis was performed using Statistica 10,0 (Stat Soft, USA). For normal distribution, data were presented as M ± SD (M is arithmetic mean, SD is standard deviation); otherwise — Me [Q1;Q3] (Me is the median value, Q1 and Q3 are the first and third quartiles). The probability of effect from a factor on a bipolar event was determined with logistic regression analysis with χ^2. The degree of correlation between test variables was evaluated with the use of Pearson correlation coefficient (r). The degree of correlation was interpreted on the basis of r value: with r = 0.01–0.29, the correlation was weak, with r = 0.3–0.69 — moderate, and with r = 0.7–1.0 — strong. Survival analysis was performed under the Kaplan–Meier method. The zero hypothesis on the absence of differences and correlations was discarded at $p < 0.05$.

Results and Discussion

The logistic regression analysis demonstrated that, among clinical and laboratory parameters, the risk of an increased IMC is statistically significantly impacted by higher SBP values, measured at the time of enrolment ($\chi^2 = 5.76$, $p = 0.016$), AH stage ($\chi^2 = 9.45$, $p = 0.002$), increased urine urea levels ($\chi^2 = 8.11$, $p = 0.004$), reduced eGFR ($\chi^2 = 5.0$, $p = 0.025$), and a higher CKD stage ($\chi^2 = 10.32$, $p = 0.001$).

The resulting data were used to generate a table of risk grading for small renal arteries (IA) remodelling in patients with GN and AH (Table 3). Of note, thickening of IA IMC was recorded where the result was equal or exceeded the median IA values (30.43 μm) in the study group (a graded parameter). The resulting logistic regression equations were used to calculate the risk of an increased IA IMC values with account of clinical and laboratory parameters.

The correlation analysis demonstrated that the IA IMC value is in direct weak correlation with the SBP values ($r = 0.29$, $p = 0.005$), AH severity ($r = 0.25$, $p = 0.01$) and moderate correlation with AH stages ($r = 0.39$, $p = 0.0001$) and CKD ($r = 0.4$, $p = 0.00008$). Also, an inverse weak correlation with eGFR was found ($r = -0.26$, $p = 0.01$).

Interestingly, higher ESR value and the degree of proteinuria did not have any statistically significant effect on IA remodelling ($p > 0.05$).

In order to achieve the objective of the study, we conducted an analysis of the effect of renal tissue changes on the risk of small renal artery remodelling. It has been shown that, among all studied parameters, a statistically significant effect on an increase of the risk of a higher IA IMC value was observed in the presence of hyaline degeneration of glomerulus anses capillaires, focal periglomerular hyaline degeneration and glomerulus sclerosis. The probability that IA IMC will be above 30.43 μm in the presence of hyaline degeneration of glomerulus anses capillaires was 31.28 % ($\chi^2 = 7.56$, $p = 0.006$), periglomerular hyaline degeneration — 33.78 % ($\chi^2 = 6.96$, $p = 0.008$), glomerulus sclerosis — 20.4 % ($\chi^2 = 3.9$, $p = 0.048$). Besides, the effect of the presence of hyaline degeneration of glomerulus anses on the risk of higher IMC values with account to GN duration (Gehan's Wilcoxon Test WW = -305.0, Test statistic = -2.097, p = 0.036, Cox-Mantel Test U = -5.66, Test statistic = -2.28, p = 0.02, Log-Rank Test WW = 5.66, Test statistic = 2.3, p = 0.02) and periglomerular hyaline degeneration (Gehan's Wilcoxon Test WW = -239.0, Test statistic = -2.07, p = 0.038, Cox-Mantel Test U = -4.67, Test statistic = -2.28, p = 0.02, Log-Rank Test WW = 4.67, Test statistic = 2.29, p = 0.02) has been established. Figures 2 and 3 show Kaplan–Mayer graphs.

An important result of the study was identification of a significant probability of an increase in IA IMC values with higher incidence of TIF ($\chi^2 = 12.16$, $p = 0.0005$) (Figure 4), and directly proportional moderate correlation between IMC and TIF ($r = 0.38$, $p = 0.0001$).

Table 3. *Stratification of the risk of an increase in the thickness of IMC MA in GN occurring with AH based on clinical and laboratory parameters*

Risk of increased IMC	Signs			
	SBP mmHg			
	100	140	160	180
Risk, %	30,7	60,6	74,1	84,2
	Hypertension, stages			
	I	II	III	
Risk, %	38,1	54,7	70,3	
	BUN, mmol/l			
	2	4	6	8
Risk, %	31,6	38,35	45,6	53,0
	eGFR, ml/min/1,73 м²			
	100	80	60	40
Risk, %	45,3	52,1	58,8	65,2
	eCKD, Ranks			
	1	2	3	4	5
Risk, %	37,3	52,6	67,5	79,5	87,9

Note: GN — glomerulonephritis, IMC MA — interlobular artery intima-media complex, SBP — systolic blood pressure, AH — arterial hypertension, eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease
The table presents the risk of IMC MA thickening, expressed as a percentage, depending on changes in clinical and laboratory parameters

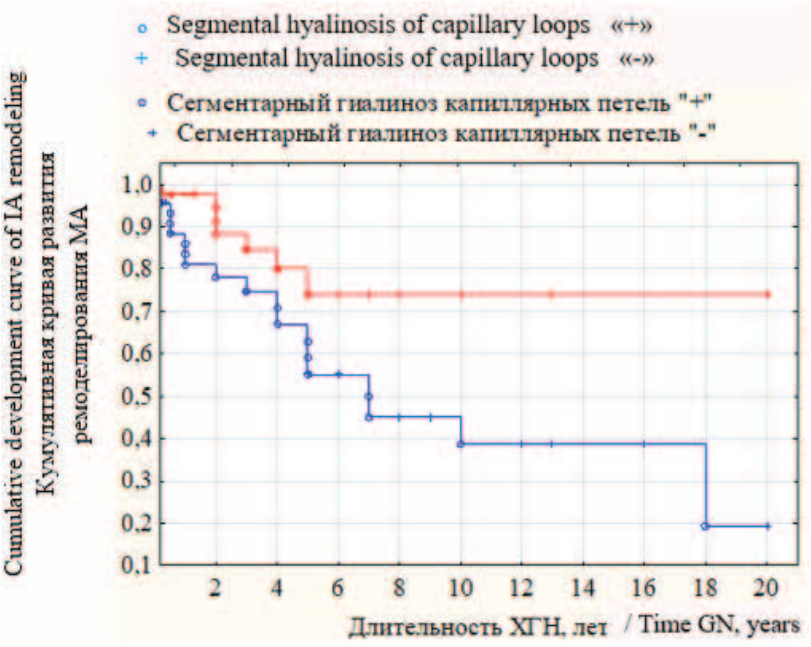

Figure 2. *Cumulative curve of MA remodeling development based on the presence or absence of segmental hyalinosis of glomerular capillary loops*

Note: the blue line is the presence of segmental hyalinosis of the glomerular capillary loops, the red line is the absence of segmental hyalinosis of the glomerular capillary loops. GN — chronic glomerulonephritis, IA — interlobular artery

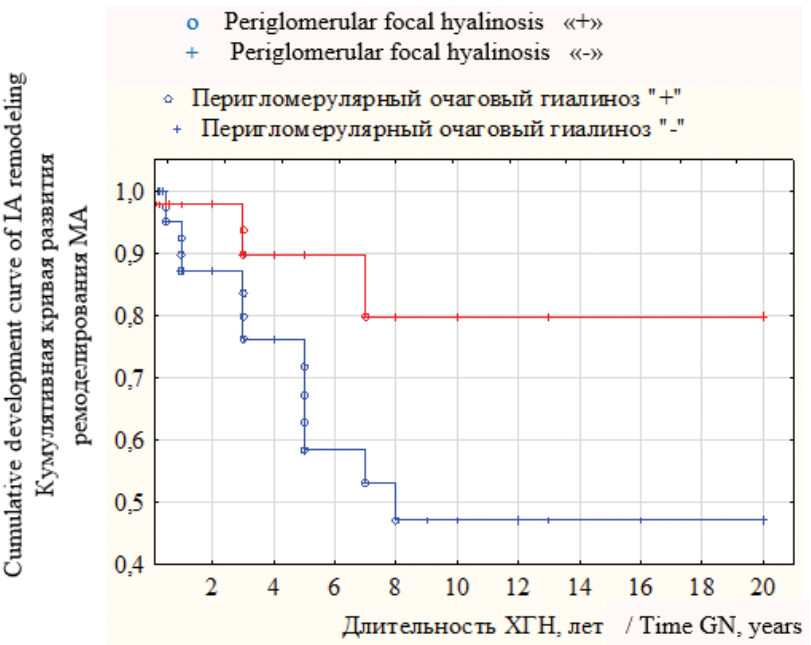

Figure 3. *Cumulative curve of IA remodeling development based on the presence of periglomerular focal hyalinosis.*

Note: blue line — presence of periglomerular focal hyalinosis, red stripe — absence of periglomerular focal hyalinosis. GN — chronic glomerulonephritis, IA — interlobular artery

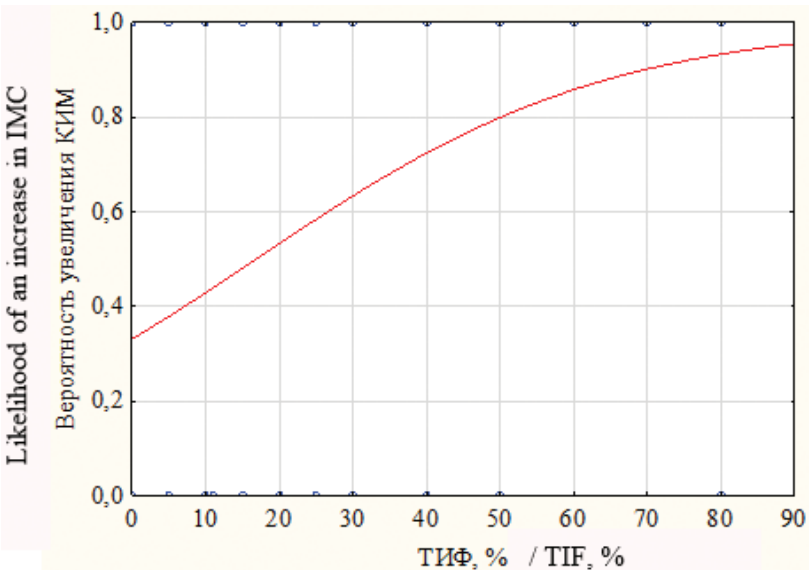

Figure 4. *Graph of non-linear logistic regression of the probability of increasing the value of intima-media complex of the interlobular artery depending on the prevalence of tubulointerstitial fibrosis and the logistic regression equation. Risk of increased intima-media complex (IMC) = exp * (-0,7 + [0,04 * tubulointerstitial fibrosis (TIF) (%)]) / (1 + exp * (-0,7 + [0,04 * tubulointerstitial fibrosis (%)])*

Note: IMC — intima-media complex, TIF — tubulointerstitial fibrosis

This study demonstrated that a condition for small artery remodelling in GN is a systemic haemodynamic factor. First, AH causes damage to arterial intima and media in any vascular pool, while systemic hypertension is an adverse prognostic factor of progressive renal tissue remodelling in numerous diseases [6, 7]. Second, it has been proven that prognosis of end-stage kidney disease in GN depends not only on glomerular damages, but also on the presence of tubular and vascular interstitial damage [8]. Numerous studies demonstrate high significance of AH as a determinant factor in the development and progression of CKD [9, 10]. However, publications on AH as a predictor of small artery remodelling in GN are scant [8, 11, 12, 13].

A publication by Zhuang Y et al. (2020) discusses analysis of factors affecting intrarenal haemodynamics remodelling in secondary GN caused by viral hepatitis B [8]. Their study evaluated the degree of small artery damage found during a morphological examination of renal bioptate. The degree of structural remodelling of the small arterial bed was used for patient grading for inclusion in the study groups. It has been shown that the most significant small artery remodelling was associated with high BP levels, serum creatinine concentrations and tubulointerstitial damage. Besides, clinical outcomes of patients with secondary GN were evaluated over a period of 94.2 ± 47.1 months. Multivariate regression analysis was used to find out that higher serum creatinine levels (1.011, 1.007–1.016), presence of AH (1.767, 1.004–3.108) and small artery remodelling (2.194, 1.062–4.530) were independent predictors of unfavourable outcomes in patients.

Another study evaluated indirect data on the condition of the microcirculation using sonographic signs in patients with CKD, 82 % of which had glomerular nephritis [11]. The study demonstrated that an increase in the resistive index in segmental and interlobar arteries directly correlated with the age (r = 0.435, p = 0.0063), pulse pressure (r = 0.303, p = 0.022), renal tissue atrophy (r = -0,275, p = 0,038) and negative correlation with impaired renal function (r = -0.402, p = 0.0018). The authors conclude that tubulointerstitial changes and impaired filtration function are most significant in the increase of resistive index of small arteries.

Identification of the correlation between small renal artery remodelling and tubulointerstitial changes and AH was described in a number of other scientific research papers with comparable results [12, 13]. However, the objective of a majority of studies was identification of the fact of renal artery changes or comparison of non-invasive kidney biopsy methods, without analysis of the association between the degree of such changes and the degree of AH.

Also, the association between glomerular and tubulointerstitial changes and signs of IA IMC remodelling has been established. In particular, it was demonstrated that as long as hyaline degeneration of glomerulus anses capillaires, focal periglomerular hyaline degeneration and glomerulus sclerosis, as well as TIF develop and progress, IA IMC remodelling becomes more common. This fact is suggestive rather of addition of vascular remodelling in GN to the overall remodelling process in renal parenchyma and is not an evidence of the effect of immune-mediated factors in GN. Apparently, the presence of AH and the association between the incidence of IA remodelling and AH duration and severity (stage and grade) make the haemodynamic effect more important for IA remodelling in GN. To be on the safe side with this hypothesis, future studies will be necessary to evaluate the condition of IA IMC in patients with GN in the absence of AH. It is likely that less marked signs of vascular remodelling in this case would be another argument in favour of the significance of the haemodynamic factor in progressive IA remodelling in patients with GN.

Conclusions

The study demonstrated that in GN with AH, the risk of small renal artery remodelling depends on the severity and stage of AH as well as duration of the disease. Also, small artery remodelling is associated with manifestations of renal tissue remodelling in GN, in the form of tubulointerstitial and glomerular fibrosis. At the same time, it has been demonstrated that the degree of proteinuria does not correlate with changes in IA IMC.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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