Hyperuricemia as a Factor Associated with the Progression of Cardiovascular Complications in Patients with Chronic Glomerulonephritis

Abstract

Purpose of the study: Define the role of hyperuricemia in the progression of cardiovascular complications in patients with chronic glomerulonephritis at predialysis stage of the disease.

Materials and methods: A total of 174 patients (132 men and 42 women) with chronic glomerulonephritis (CGN) aged 17 to 71 years at predialysis stage of the disease were examined. Depending on plasma uric acid concentration (PUAC), patients were divided into two groups (Group 1: level PUAC ≥ 0.490 mmol/L, Group 2: ≥ 0.420 mmol/L). The groups were comparable by gender, age, disease duration, hemodynamic parameters and lipid profile. Along with clinical and laboratory studies, all patients underwent echocardiographic assessment of structural changes of heart.

Results: Patients in Group 1 noted a significant reduction in glomerular filtration rate (GFR) (37.9 (21.4-68.3) mL/min versus 63.4 (29.0-87.6) mL/min; p = 0.016) in increase in plasma creatinine (175 (128-368) mmol/l versus 138 (106-247) mmol/l; p = 0.036), an increase of left ventricular myocardial mass index (180.7 ± 64.2 g/m² vs. 163.6 ± 75.5 g/m²; p = 0.033) and right ventricular longitudinal dimension (2.02 ± 0.39 cm vs. 1.90 ± 0.34cm; p = 0.041) compared to the 2nd group. Eccentric type of LV myocardium hypertrophy was significantly more often detected in group 2, and concentric type of LV - in the 1st group. Positive correlation between the content of PUAC and LV myocardial mass index (r = 0.168; p = 0.035) and negative correlation between the content and value of GFR (r = 0.202; p = 0.011) was detected in general group. Direct correlation between elevated levels of PUAC and diastolic blood pressure value in both groups 1 and 2 (r = 0.252; p = 0.049 and r = 0.241; p = 0.017, respectively) was statistically significant.

Conclusion: In patients with chronic glomerulonephritis at predialysis stage of the disease, increased plasma uric acid concentration involves substantial slowdown of glomerular filtration rate, on the one hand, and structural changes in geometry of the left ventricle, on the other.

Keywords: Chronic glomerulonephritis; Uric acid; Cardiovascular complications; Left ventricle

Introduction

The question of the mechanisms of the progression of cardiovascular complications (MTR) in chronic glomerulonephritis (GV) is one of the central in modern nephrology [1-3]. Among non-immune factors associated with the progression of GBV, an important role is played by hyperuricemia [1,4]. As early as 1948, M. Tareyev wrote in his monograph “Hypertonic Disease” about the frequent combination of arterial hypertension (AH) and metabolic disorders, including not only lipid and carbohydrate disturbances, but also purine metabolism [6]. It is well known that a decrease in the glomerular filtration rate (GFR) is accompanied by a slowing of the uricosauric function of the kidneys. Uric acid (MC) has the ability to initiate and maintain endothelial dysfunction, as well as stimulate the proliferation of smooth muscle cells, both in the systemic vascular bed and in the renal vessels [4,7]. Along with this, the widespread use of loop, thiazide diuretics and cyclosporine [1,8,9] also has a significant effect on the degree of excretion of uric acid in chronic kidney disease (CKD). In addition, at the stage of pronounced decrease in the nitrogen excretory function of the kidneys, AH occurs in almost every second patient [1,2]. Cardiovascular risk in GBV is increased several hundred fold, and finding out the pathogenetic mechanisms of heart damage is of great practical importance in the development of new therapeutic strategies for preventing and/ or reducing adverse cardiac complications in the stage of dialysis therapy [1,2,10,11]. In this connection, the purpose of the present work was to study the role of hyperuricemia in the progression of cardiovascular complications in the course of the pre-dialysis stage of the disease.
Object and Methods of Research

A one-stage study included 174 patients (132 men and 42 women) aged 17 to 71 years, with established diagnosis of chronic GBV at various stages of chronic kidney disease (CKD). The average age of the patients at the time of the examination was 42.6 ± 13.0 years. Depending on the level of uric acid, the subjects were divided into two groups: the first group included 69 patients with a plasma MK level of ≥0.490 mmol/L, and the second group had plasma MK content ≥ 0.420 mmol/L and <0.490 mmol/L. All patients underwent clinical and biochemical blood tests. The criteria for inclusion in the study were patients with GB at different pre-dialysis stages of CKD. From the study, individuals with CKD who were in the stage of dialysis therapy, as well as those suffering from connective tissue diseases were excluded. A more detailed description of the patients included in the study is presented in Table 1.

All patients underwent a comprehensive examination with verification of the diagnosis. Laboratory tests included determination of hemoglobin (Hb) level, mean hemoglobin content in erythrocytes, hematocrit, erythrocyte count, lipogram, electrolytes, fibrinogen, total and C-reactive protein level, serum creatinine and 24-hour urinary protein excretion. The functional state of the kidneys was assessed on the basis of a survey of patients with the definition of the glomerular filtration rate (GFR), calculated by the formula EPI and K / DOQI [12]. The character of the structural changes in the heart was detected with the help of a non-invasive ultrasound echocardiographic (EchoCG) study on the ultrasonic device “Sequoia 512” of the corporation “Siemens-Acuson” (Germany, USA) according to the generally accepted method. At the same time, the wall thickness, left ventricle (LV) cavity dimensions, left atrial diameter (cm) were assessed from parasternal access along the long axis of the LV. Measure the thickness of the interventricular septum (MZHP, cm) and the posterior wall of the left ventricle (LZWR, cm) in the diastole, the end diastolic (CDR, cm) and the final systolic dimensions (KS, cm) of the LV were determined. The ejection fraction (FV,%) was also investigated. The LV myocardial mass (LVMM) was calculated by the formula R.B. Devereux et al. (1986): MMMLZH (g) = 0.8 x {1.04 - (KDR + MZV + LZZL) 3 - KDR3} +0.6. The LV myocardial mass index (LVMMI) was defined as the ratio of LVDM to body surface area. Criteria for left ventricular hypertrophy (LVH) and types of myocardial remodeling were determined in accordance with the recommendations of the EOK from 2013 [13]. To evaluate LVH, LVMM was calculated, the upper value of which was 95 g/m² for women, 115 g/m² for men. The relative wall thickness (OTS) of the LV was calculated for each patient as (MZV + LZZL) / LVD. For the increase in OTS, the value was more than 0.42 units [13]. Depending on the size of LVMM and OTS, the following types of structural state of LV geometry were distinguished: normal LV geometry (OTS <0.42, normal LVMMI), concentric remodeling (OTS> 0.42, normal LVMMI), concentric hypertrophy (OTS> 0.42, LVMMI is more than normal), eccentric hypertrophy (OTS>0.42, LVMMI is more than normal).

The statistical processing of the material was carried out using the licensed package of programs Statistica 6.0. The significance of the differences between the groups was assessed using the Student’s t-test (for variables with normal distribution) and the Mann-Whitney test (for variables with nonparametric distribution). Data are presented as mean ± standard deviation for variables with normal distribution, median (25% -75%) for variables with non-parametric distribution. To assess the correlation relationship, the Pearson method was used. The level of statistical reliability was considered to be p <0.05.

The Results of the Study and their Discussion

Table 1 shows the distribution of the examined patients with GB on the severity of renal dysfunction. It follows from this that at all stages of CKD, the proportion of men with GB is significantly more prevalent. This fact is explained by the fact that, traditionally, male subjects more often suffer from glomerular kidney diseases.

It is important to emphasize that initially patients of both groups in terms of age, sex, duration of the disease, parameters of anthropometry, indices of central hemodynamics and peripheral blood did not differ significantly (Table 2). However, a clinically perceptible downward trend occurred from the hemoglobin concentration (Hb), i.e. in the group of persons with a high content of MK plasma, the average value of Hb was 130.9 ± 27.1 g/L compared to 136.1 ± 24.9 g/L (group 2). The effect of Hb content on the rate of progression of nephropathy was established in a series of studies [14,15]. On the contrary, timely detection and treatment of anemia in CKD, especially in the pre-dialysis stage, significantly improves prognosis, while reducing the connection of cardiovascular complications (MTR) [1,2,11].

The data presented in Table 3 show that the compared groups with respect to lipid profile, total and C-reactive protein, fibrinogen and blood electrolytes did not differ significantly. Attention is drawn to the fact that the number of patients with a high content of fibrinogen significantly prevailed in the 1st group, ie, in patients with a high plasma MK level (Table 3), which agrees with the literature data [5]. The increase in the level of proinflammatory proteins in CKD triggers a number of pathophysiological changes, including the association of inflammatory markers with the development of LVH, which was explained by the effect of C-reactive protein on the activation of angiotensin II receptors, which contributes to the development of endothelial dysfunction [16].

The level of MK of blood serum is also closely related to violations of lipid metabolism, obesity and the risk of developing MTR [1,6]. In persons with AH, an increase in MC content by 1 mg/dL is accompanied by an increase in MTR by 10%, an increase in systolic blood pressure by 10 mm Hg, Art. and the development of hyperlipidemia [17]. In turn, the listed risk factors for the development of CCO in the population of people with CKD accelerate the processes of nephrosclerosis. Discussing the data presented in Table 3, it should be noted that in the 1st group there was a significant increase in the plasma creatinine concentration [175 (128-368) μmol/l versus 138 (106-247) μmol/l; p = 0.036] and a palpable retardation of GFR [37.9 (21.4-68.3) ml/min versus 63.4 (29.0-87.6) ml/min; p = 0.016] in comparison with the 2 nd group. It is noteworthy that the value of the daily excretion of the protein in both the 1 st and 2 nd group was practically

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similar. The results obtained from Table 3 indicate that the drop in the nitrogen excretory function of the kidneys is accompanied by a significant increase in the concentration of MK of the blood serum. In experimental models of kidney damage in five of the six nephrectomies, cyclosporine and angiotensin II mediated nephropathy, pharmacologically induced hyperuricemia accelerated the development of nephrosclerosis and facilitated the slowing of glomerular filtration. In the meta-analysis, which includes more than 700 patients, there is undeniable evidence of the beneficial effect of treatment that reduces the level of MK in the blood on the rate of progression of CKD. Decreased MC content on the background of therapy with xanthine oxidase inhibitors in individuals with renal dysfunction promoted the growth of GFR and decreased plasma creatinine level [18]. In turn, the positive effect of the normalization of MK indices on renal function in patients receiving xanthine oxidase inhibitors was accompanied by a reduction in the risk of developing MTR [16,19].

Table 1: Characteristics of patients included in the study.

| Indicators          | Stages of chronic kidney disease, K / DOQI, 2002 |
|---------------------|-----------------------------------------------|
|                     | 1     | 2     | 3a    | 3b    | 4     | 5     |
| Total, n            | 35    | 45    | 16    | 26    | 32    | 20    |
| Men n               | 29    | 35    | 11    | 18    | 26    | 13    |
| Women, n            | 6     | 10    | 5     | 8     | 6     | 7     |

Note: K / DOQI - Kidney Disease Outcomes Quality Initiative.

Table 2: Clinical and laboratory characteristics of patients included in the study.

| Options                          | 1st Group (n=69) | 2nd Group (n=105) | P=   |
|----------------------------------|------------------|-------------------|------|
| Age, years                       | 41,9±12,6        | 43,1±13,3         | 0,555|
| Sex, husband/wife                | 50/19            | 82/23             | 0,228|
| Duration of disease, years       | 6 (3-12)         | 5 (2-10)          | 0,826|
| Weight, kg                       | 77,5±15,2        | 78,7±16,6         | 0,633|
| Body mass index, kg/m²           | 27,3±4,8         | 27,5±5,26         | 0,828|
| Number of heartbeats, in min.    | 75±10            | 76±12             | 0,687|
| Blood pressure (C), mm Hg. Art.  | 143±25           | 145±24            | 0,623|
| Blood pressure (D), mm Hg. Art.  | 90±13            | 90±13             | 0,978|
| Blood pressure (mean), mm Hg. Art.| 47±8            | 48±17             | 0,623|
| Blood pressure (P), mm Hg. Art.  | 52±15            | 54±15             | 0,447|
| Hemoglobin, g/l                  | 130,9±27,1       | 136,1±24,9        | 0,203|
| Hematocrit, %                    | 43,6±9,06        | 45,3±8,33         | 0,203|
| Erythrocytes, x10¹²/l            | 4,35±0,64        | 4,47±0,53         | 0,173|
| Average hemoglobin content, pg   | 29,8±2,28        | 30,1±2,45         | 0,340|

Note: C: Systolic; D: Diastolic; P: Pulse; P: Reliability.

Table 3: Biochemical and functional parameters of the groups examined.

| Options                | 1st Group (n=69) | 2nd Group (n=105) | P=   |
|------------------------|------------------|-------------------|------|
| Uric acid, mmol/l      | 0,553±0,053      | 0,451±0,023       | 0,000|
| Cholesterol, mmol/L *  | 5,31 (3,91-6,86)| 5,52 (4,47-7,01) | 0,442|
| HDL-C, mmol/L *        | 1,0 (0,70-1,25)  | 0,9 (0,8-1,30)   | 0,911|
| LDL-C, mmol/L *        | 3,15 (2,34-4,24)| 3,56 (2,63-4,44) | 0,226|

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The next stage of the present study was a structural analysis of echocardiographic parameters in the individuals surveyed, as reflected in Table 4. A noticeable tendency for anterior-posterior size of the left atrium and the thickness of the interventricular septum was observed in the 1st group. Simultaneously, in the same group, a statistically significant increase in the level of the LV myocardial mass index (180.7 ± 64.2 g/m² vs 163.6 ± 75.5 g/m², p = 0.033) was found in comparison with the second group. In addition, an analysis of the structural modification of the LV geometry showed a marked reduction in the number of patients with normal LV geometry and an increase in cases of concentric hypertrophy of the LV in the 1st group. While in the 2nd group, the eccentric type of LV hypertrophy was significantly more frequent. It is important to note that in the 1st group the longitudinal size of the right ventricle was significantly higher (2.02 ± 0.39 cm vs. 1.90 ± 0.34 cm, p = 0.041) compared with group 2.

Table 4: Echocardiographic indices in the examined groups.

| Indexes                        | 1st Group (n=69) | 2nd Group (n=105) | P=   |
|--------------------------------|-----------------|------------------|------|
| Left atrium, cm                | 3.65±0.56       | 3.50±0.41        | 0.056|
| CD size of the left ventricle, cm | 5.24±0.61         | 5.15±0.39        | 0.261|
| CS size of the left ventricle, cm | 3.47±0.70         | 3.36±0.41        | 0.201|
| Fraction of ejection of the left ventricle, % | 61.7±9.69           | 63.4±5.30        | 0.138|
| Thickness of MZP, cm            | 1.05±0.23       | 0.99±0.17        | 0.054|
| Thickness of LCPV, cm           | 1.02±0.20       | 0.97±0.14        | 0.113|
| Indexed LVML, g/m²              | 180.7±64.2      | 163.6±75.5       | 0.033|
| Relative wall thickness, unit   | 0.39±0.08       | 0.38±0.06        | 0.214|
| Normal LV geometry, n           | 1               | 7                | 0.000|
| Concentric remodeling, n       | 9               | 2                | 0.000|
| The eccentric type, n           | 42              | 79               | 0.000|
| Concentric type, n             | 20              | 14               | 0.311|
| Right ventricle, cm             | 2.02±0.39       | 1.90±0.34        | 0.041|
| The anterior wall of the right ventricle, cm | 0.39±0.03           | 0.39±0.02        | 0.432|

Note: CD is the terminal diastolic; COP: Terminal Systolic; MZHV: Interventricular Septum; ZVLZH: Posterior Wall of the Left Ventricle; MMLZH: The Mass of Myocardium of the Left Ventricle; P: Reliability.

In the available literature, we have not found work that examines the state of the right heart in people who suffer from GB at the pre-dialysis stage of the disease. At the same time, it has been established that remodeling of LV in the form of concentric hypertrophy in persons with AH serves as a predictor of unfavorable MTR [20,21], and the development of eccentric type of LV hypertrophy in the presence of GF contributes to the persistence of symptoms of heart failure and the occurrence of cardiac arrhythmias [1]. Most clinical studies also show that in CKD, in response to volumetric overload of the LV, the eccentric...
model of LV hypertrophy is revealed, mainly on echocardiography. If the left heart is experiencing pressure overload, then concentric variants of changes in LV geometry are registered [2].

To assess the effect of the concentration of plasma MK on the development of cardiovascular risk, a correlation analysis was performed in the individuals examined by us, the results of which are reflected in Table 5. It shows that a significant correlation is observed between the content of the MK of the blood and GFR ($r = 0.202, p = 0.011$) and LVMI ($r = 0.168, p = 0.035$). This fact completely agrees with the results of other studies [404], which shows a direct correlation between the increase in the level of MC and the increase in LVMI. There was a weak, unreliable relationship between the content of MC and the longitudinal size of the right ventricle ($r = 0.150, p = 0.059$). In our opinion, this is probably due to the small sample size included in the correlation analysis. In many clinical and epidemiological studies, the independent role of hyperuricemia in the development of AH and CKD was established [22-26]. In this connection, we carried out an additional correlation analysis within each group to clarify the above-mentioned fact. At the same time, we were able to demonstrate the presence of a reliable relationship between the elevated MC level and the value of diastolic blood pressure in both study groups ($r = 252, p = 0.049$ and $r = 241, p = 0.017$, respectively).

Table 5: Correlation analysis between clinical and laboratory parameters and the content of uric acid.

| Indicators                                           | Uric acid of plasma, μmol / l |
|-----------------------------------------------------|-------------------------------|
|                                                     | R                | P=       |
| Body mass index, kg/m²                               | -0.180            | 0.823    |
| Systolic blood pressure, mm Hg. Art.                 | 0.029             | 0.714    |
| Diastolic blood pressure, mm Hg. Art.                | 0.395             | 0.622    |
| Calculated velocity of CF, ml/min                    | -0.202            | 0.011    |
| Proteinuria, g/s                                     | 0.096             | 0.229    |
| Right ventricle (longitudinal dimension), cm         | 0.150             | 0.059    |
| Indexed mass of LV myocardium, g/m²                  | 0.168             | 0.035    |

Note: Blood pressure; CF: Glomerular Filtration; LV: Left Ventricle. R is the rank correlation coefficient; P: Reliability.

It is noteworthy that the data obtained by us confirm the results of a prospective study, where a close association between the level of MC and diastolic blood pressure was revealed [27]. The pathogenetic relationship of hyperuricemia and AH has also been demonstrated in a number of experimental studies on animals. Thus, R.J. Johnson and co-authors have shown that a moderate increase in the level of MC can lead to glomerular-tubular lesions followed by activation of the renin-angiotensin-aldosterone system (RAAS) and an increase in blood pressure. At the same time, all changes underwent the reverse development after elimination of hyperuricemia [28]. In another experimental work on rats, T. Nakagawa and co-authors revealed a clear relationship between mild hyperuricemia and renal glomerular hypertrophy through activation of RAAS. It was found that when the MC level was increased by 1 mg/dL, systolic blood pressure increased by 30 mm Hg. Art. and hypertrophy of the glomerular mesangium developed. MK enters the smooth muscle cells of the vessels through specific channels, triggering the activation of kinases, nuclear transcription factors, cyclooxygenase-2, the production of growth factors and inflammatory proteins [16,30]. As a result of such autocrine stimulation, proliferation of smooth muscle cells, thickening of the vascular wall, loss of vascular elasticity, and sodium narsus also change, as a result of the development of sodium-dependent AG. The increase in the content of MC plasma serves as a predictor of development of hypertension [5,30]. Conversely, a decrease in MC concentration can reduce blood pressure and prevent the development of AH complications [31,32]. Based on the analysis of literature data and the results obtained by us, it may be concluded that it is necessary to monitor the parameters of uricosauric renal function even at pre-dialysis stages of glomerulonephritis, which will help in inhibiting the formation of cardiovascular complications in the future (at the stage of hemodialysis therapy).

Thus, our study shows that as the concentration of MK in increases, serum glomerular filtration slows down significantly, there is a tendency to decrease the hemoglobin content and increase the number of patients with hyperfibrinogenemia. The association of hyperuricemia with low renal nitrogen excretion significantly accelerates the development of unfavorable geometric types of LV remodeling, as well as structural changes in the right ventricle.

Conflict of Interest

None of the authors have no conflicts of interest.

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