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Proteinuria and cardiovascular risk at chronic glomerulonephritis

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Abstract

Abstract Objective: To study the role of nephrotic proteinuria in the light of reno-cardiac interactions upon chronic glomerulonephritis (CGN) at an early stage of the disease.**Material and methods:** 143 patients with CGN were examined: 70 patients with a daily proteinuria of <3.5 g and 73 patients with a daily proteinuria of > 3.5 g. All patients were subjected to general clinical examination. **Results**: Lower values of erythrocytes and platelets counts, lower concentrations of Hb and total protein were detected in the plasma of patients with nephrotic proteinuria. In addition, they had higher contents of total cholesterol, LDL cholesterol, triglycerides and fibrinogen concentration. It was found that linear heart sizes were increased upon heavy proteinuria (LA 3.1 ± 0.3 cm against 3.0 ± 0.3 cm, p <0.05), LV ESS (3.1 ± 0.3 cm against 3.0 ± 0.2 cm, p<0.05), LV EDS (4.9 ± 0.3 cm vs 4.7 ± 0.3 cm, p<0.05) and indexed left ventricular mass (138.5 ± 24.6 g/mI against 130.5 ± 18.8.5 g/mI, p<0.05) as compared to patients with proteinuria of < 3.5 g per day.. Correlation analysis showed that there is close negative relationship between indexed left ventricular mass and Hb concentration and platelet counts, as well as the positive correlation relationship between indexed left ventricular mass and the value of daily proteinuria in the 2nd group. **Conclusion**: Availability of nephrotic proteinuria in patients with CGN is associated with the increase in indexed left ventricular mass and left ventricular cavities.

Keywords: chronic glomerulonephritis, proteinuria, left ventricle, cardio-vascular diseases

Introduction

Today chronic kidney disease (CKD) is one of the most important medical and social problems of modern nephrology.It is related to extremely high prevalence of this disease, predominance

thereof among the persons of working age as well as tosteady progression of CKD, which causes early population disability [1,6,8]. Chronic glomerulonephritis (CGN) holds a leading position in the CKD structure.In 2002 in Kyrgyzstan, prevalence of CGN and nephrotic syndrome amounted to 34.2 per 100 000 population. It should be also noted that the index has increased to 61.9 cases per 100 000 population by 2011. It is generally recognized that majority of patients suffering from CGN do not live till terminal renal insufficiency and die from cardiovascular complications(CVC) [16.7]. Cardiac events are often accompanied by the course of CGN. In many medical cases, these processes develop in parallel. In this case, recent researches give an important role to timely elimination of "renal factors" of risk of cardiac pathologies origination, the leading position among which is given to the proteinuria [13, 23].It should be noted that the majority of clinical researches are known to study the influence of proteinuria on CVD in patients with secondary nephropathy, that is, on the population of people suffering from pancreatic diabetes (PD)and arterial hypertension (AH) [21]. At the same time, contribution of nephrotic proteinuria into development of CVC in patients of youthful stage with CGN at early stages of disease is studied incompletely.

Study objective: To study the role of nephrotic proteinuria in the light of reno-cardiac interactions upon chronic glomerulonephritis (CGN) at an early stage of the disease

Materials and methods:the work is performed on the base of specialized nephrology department of the Mirsaid Mirralhimov National Center for Cardiology and Therapy. The study covered 143 patients with nephrotic form of CGN at the early stage of disease, 70 patients out of which (42 men, 32 women, average age 29.2±10.7 years old) with proteinuria value of less than 3.5 grams per day and 73 patients (51 men, 22women, average age 32.8±12.0 years old) with more than 3.5 gram of daily protein excretion upon the absence of edema syndrome. Average duration of disease amounted to 4 (2-9) years, both groups could be compared under age, haemodynamics parameters and kidneys functions. The study did not coverthe persons having hypertonic and mixed form of CGN, coronary heart disease, cardiac conduction and rhythm disturbance, heart failure, systemic diseases of connective tissues, pancreatic diabetes, liver and blood pathology.All the patients were subjected to a set of clinical and laboratory and instrumental examinations. Anthropometric measurement included measurement of height, weight through identification of body mass index. Heart rate, level of systolic, diastolic, average andpulse arterial pressure were measured using generally accepted method. Laboratory analyses included identification of hemoglobin concentration (Hb), erythrocytes and platelets counts in blood and biomedical measurements {concentration of lipids, fibrinogen, total protein, creatinine, glomerular filtration rate (GFR) and daily proteinuria}. All patients were also subjected to electro and echocardiographic examination where linear heart sizes {left atrium, end-systolic and end-diastolic size of left

ventricular (LV), thickness of interventricular septum, LV rear wall}, left ventricular mass were evaluated under the formulae of R. Devereuxet. al.[10]. Data was subjected to statistical processing on the personal computer Windows 2007 in the medium of Excel spreadsheets using the application programs package “Statistica 6.0”. Significance of differences between groups was assessed with the help of Student's t-test (for variables with normal distribution) andMann-Whitney test (for variables with non-parametric distribution). Data has been represented as an average ± standard deviation for variables with normal distribution, median (25% - 75%) for variables with non-parametric distribution. Non-parametric correlation analysis was used under the Spirman’s method to identify relation between measurements studied. The value of $p<0.05$ was considered to be the level of statistical significance.

Results and discussion

As it was already noted, examined groups could be compared under age, duration of a disease, weight and BMI, arterial pressure level (table 1). However, according to dividing criteria,measurements of daily proteinuria showed appreciable difference. It is necessary to point out that there wasa trend of increase both in systolic and diastolic level of AP in patients having nephrotic proteinuria.

Analysis of kidneys’ functional statusbetween examined groups has not revealed significant differences, as all patientscovered by the study were ill for relatively short period.

Table 1

It is considered that the presence of proteinuria even in default of AH and PD in patients with CKD is always characterized by big degree of CVC development as compared to general population [13,18].

The proteinuria independently causes changing of canaliculi and interstitial tissues of kidneys along with the risk factors such as hyperlipidaemia and anemia [7]. Eventually, appearance and progression of interstitial fibrosis causes activation of angiotoninII gratuitous synthesis in kidneys, which probably induces AH development [9] in addition. The study conducted by LIFE showed that increased protein excretion together with urine was clearly associated with LV hypertrophy regardless of AP level, presence of pancreatic diabetes, content of creatinine in blood serum, age, sex, race and addiction to smoking [22].

As it is known, nephrotic proteinuria make a decisive contribution into CGN progression. Anemiadevelopment is also related to it at the early stages of disease. Thus, persistent proteinuria is not only an activity index of renal process but also is a factor causing gland deficiency development due to loosing of transferring with urine, inefficiency of folic acid, B_{12}vitamin as well as due to

abnormality of suction processes indigestive tract [14]. According to the data of M.C. Thomas [20], patients having 2nd type PD with proteinuria andrenal failure were noted to have Hb level depression to 1-2 g/dlper year, which was not noted in patients suffered from 2nd type PD with no proteinuria and renal failure. Hb value of those patients remained stable within subsequent five years of observation. Thomas showed that fall in blood Hb to more than 2 g/dl per year was observed in half of patients sick with proteinuria and only in 10% of patients with secured nitrogen releasing functions of kidneys. The table 2demonstrates the results of erythrocytes analysis. One can see from the table that Hb concentration, counts of erythrocytes and platelets were significantly lower in 2nd group's patient, that is with more than 3.5 grams proteinuria value. Clinical studies have proved that Hb content is more likely to fall in the presence nephrotic proteinuria than in patients having no proteinuria [14]. It is also established that there is often high risk of anemia development even under secured values of GFR upon big values of proteinuria [18].

Table 2

It can be confirmed by the correlation analysis results, where negative interrelation between proteinuria and Hb concentration ($R= -0.17$, $p<0.03$), red blood count ($R= -0.20$, $p<0.01$) was noticed in the 2nd groups of persons with nephrotic proteinuria, whereas such interrelation was not noticed in the 1st group.We have earlier showed presence of negative correlation between proteinuria degree and red blood count in patients with nephrotic glomerulonephritis [5]. Accelerated development of anemia under nephrotic proteinuria is due to that the filtered and re-absorbed protein causes tubular andinterstitial cells proliferation, emission of chemokines and cytokines by the same, which intensify formation of intracellular matrix [6.15]. If there is excess amount of proinflammatory cytokines, it makes favor not only for the erythropoetin secretion suppression in kidneys, but also for reduction of its erythropoietic activity in bone marrow [8].Early detection and correction of these factors under CGN remains as important and integral task of modern nephrology.

Table 3

While considering biochemistry indices (table 3) in the groups of patients with CGN and nephrotic proteinuria examined by us, we have detected lower content of blood total protein and higher levels total cholesterol, LDL cholesterol, triglycerides and fibrinogen. Development of hypoproteinemia, hyper and dislipidemy, hyperfibrinogenemia at nephrotic glomerulonephritis is generally known. Another important factor for CGN progression is dislipidemy [3]due to both atherosclerotic affection of renal vessel and direct nephrotoxic effect of lipids.It is established that if nephrotic syndrome lasts for a year, hypercholesteremia is accompanied by reduction of five-year

«kidney» survival from 90% to 62% [2].Cells that have receptors to cholesterol LDLbind and acidify them by launching further generation of cytokines, which stimulate proliferation in mesangium andnephrosclerosis development. Generation of proteoglycans and collagenolytic ferments that regulate mesangial matrix formation is decreased in parallel, phagocytic properties of deep cells are weakened, mesangium is «overloaded» with macromolecules. Lipoproteins,deposited on the cells' basic membrane, bind negatively charged glycosaminoglycans and neutralize its negative chargeby raising penetrability of the membrane for protections, which results in proteinuria progression.

Table 4

In order to study structural changes in cardiac muscle in patients with CGN, we have also analyzed echocardiography parameters (table 4), where LA and LV sizes turned out to be larger in patients with nephrotic proteinuria except for LV wall thickness. Besides it, we have also noted gain in ILVM in patients with proteinuria. During the correlation analysis we have detected interrelation between ILVM, Hb concentration ($r=-0.45$, $p=0.005$), platelets count ($r=0.34$, $p=0.05$), triglycerides ($r=0.26$, $p=0.05$) andvalue of protein excretion with urine ($r=0.25$, $p=0.05$). Gain inLVM in patients with PD at the state of proteinuria was also shown in researches of S.I. Popov and others [4], where they distinguished coronary blood flow decrease, confirmed by the myocardium perfusion scintigraphy.

Results of the great number of researches demonstrated that microalbuminuria was precursory symptom of renal irritation under AH, diabetic nephropathy and reflected initial stages of vessels pathology (endothelial disfunction, atherosclerosis) and constantly correlated with increase in CVD and mortality rate [17]. Even small levels of proteinuria are clearly related to increase of risk of cardiovascular events[19].

Thus the research performed by us testifies that indexed left ventricular mass increases in patients suffering from chronic glomerulonephritis if there is nephrotic proteinuria.

Table 1

Clinical profile of examined patients

Indices	Proteinuria <3.5g/s (n=70)	Proteinuria >3.5 g/s (n=73)	p<
Age, years	29.2±10.7	32.8±12.0	0.06
Duration of disease*, years	3 (2-9)	6 (2-9)	n/a
Sex, male/female	42/38	51/22	n/a
Body mass, kg	62.1±10.0	65.1±11.2	n/a
BMI, kg/m²	21.8±2.3	22.4±1.8	n/a
Heart rate, beats per minute	74.5±11.0	79.8±10.3	n/a
AD (S), mm hg	119±16	123±18	n/a
AD (D), mm hg	78,2±10,3	81,3±9,8	0.06
AD (Av), mm hg	91.9±11.4	95.3±11.7	n/a
AD (P), mm hg	41.2±10.0	42.0±12.5	n/a
Creatinine*(micromole)	84 (70-97)	84 (67-108)	n/a
Proteinuria *, мg/day	837(243-2.096)	7551(5.208-12.586)	0.05
GFR *, ml/min	112.4±47.3	106.8±48.0	n/a

Note:*- data presented asa median (25%-75%); BMI- Body mass index; AD – arterial pressure; S – systolic; D – diastolic; Av – average; P – Pulse; GFR – glomerular filtration rate;

Table 2

Red blood values in examined groups

Values	proteinuria<3.5g/s (n=70)	proteinuria >3.5 g/s(n=73)	p<
Hemoglobin, g/dl	142.7±20.3	134.9±20.8	0.05
Erythrocytes, mln/mcl	4.63±0.46	4.43±0.45	0.05
Thrombocytes, mln/mcl	250.3±23.2	239.1±27.5	0.05

Table 3

Biomedical measurements in examined groups

Values	proteinuria<3.5g/s (n=70)	Proteinuria>3.5 g/s (n=73)	p<
Blood serum iron, (micromole)	18.7±7.0	17.4±7.8	n/a
Total protein, g/l	59.7±12.4	43.4±10.1	0.05
Total Ch, (mM/l)	5.06±2.0	8.45 ± 3.66	0.05
Cholesterol HDL, (mM/l)	1.11±0.41	1.17±0.42	n/a
Cholesterol LDL*, (mM/l)	2.7 (2.1-3.7)	5.2 (3.7-8.2)	0.05
TG*, (mM/l)	1.7 (1.0-2.1)	2.2 (1.8-3.6)	0.05
Fibrinogen *, (mg/ml)	4660.5 (3108-6660)	7659 (5772-10656)	0.05
PTI *, (%)	88 (79-96)	83 (79-100)	n/a

Note:*- data presented as a median (25%-75%); Cholesterol HDL – cholesterol of high-density lipoprotein; cholesterol LDL – cholesterol of low-density lipoproteins; TG- triglycerides; PTI – prothrombin index

Table 4

Echocardiographic indices in examined groups

Indicators	proteinuria <3.5 g/s (n=70)	proteinuria >3.5 g/s (n=73)	p<
LA, cm	3.0±0.3	3.1±0.3	0.05
ESSLV, cm	3.0±0.2	3.1±0.3	0.05
EDS LV, cm	4.7±0.3	4.9±0.3	0.05
LVEF, %	66.4±3.4	65.9±3.8	n/a
IVST, cm	0.82±0.08	0.84±0.08	n/a
TLVRW, cm	0.81±0.08	0.83±0.11	n/a
RV, cm	1.75±0.32	1.79±0.36	n/a
FWRV, cm	0.36±0.4	0.38±0.4	n/a
LVM, g	221.7±43.3	247.7±57.8	0.05
ILVM, g	130.5±18.8	138.5±24.6	0.05

Note: LA– left atrium; ESS – end systolic size; EDS – end diastolic size; LVEF – left ventricular ejection fraction; IVST– interventricular septum thickness; TLVRW– thickness of left ventricular's rear wall; RV - right ventricle; FWRV – front wall of right ventricle; LVM – Left Ventricular Mass; ILVM – indexed left ventricular mass.

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