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N. V. Gubina https://orcid.org/0000-0001-6049-8865
I. H. Kupnovytska https://orcid.org/0000-0002-6997-460X
N. M. Romanyshyn https://orcid.org/0000-0002-0243-2638

CYSTATIN C AND LIPOCALIN-2 AS BIOMARKERS OF INITIAL RENAL DYSFUNCTION WITHIN THE RENAL-METABOLIC CONTINUUM

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

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N. V. Gubina, I. H. Kupnovytska, N. M. Romanyshyn

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The relevance of the problem of kidney damage in patients with obesity is due to the increase in the frequency of nephropathies associated with metabolic disorders.

The aim of the study is to evaluate changes in lipocalin-2 in urine as an early biomarker of renal dysfunction against the background of obesity and its relationship with cystatin C and the HOMA-IR index in such patients.

Materials and methods. 300 patients with chronic kidney disease were examined. The patients were divided into 4 groups: group 1 (70) – patients with stage 1 CKD and normal body weight, group 2 (72) – patients with stage 2 CKD and normal body weight; group 3 (70) – patients with 1 stage CKD and obesity, group 4 (88) – patients with stage 4 CKD and obesity. The control group consisted of 30 apparently healthy individuals. BMI was determined for all patients, glomerular filtration rate (GFR) was calculated according to CRD-EPI formulas based on the level of creatinine, cystatin C and their combination (CRD-EPIcysC/cr) (ml/min/1.73 m^2). The level of cystatin C in blood serum and lipocalin in urine was determined by enzyme immunoassay methods. The HOMA-IR index was determined by the immunochemiluminescence method and calculated according to the formula. Establishment of the level of glycosylated haemoglobin (HbA1c) was carried out by the spectrophotometric method.

Results. In groups of patients with CKD and obesity, the level of lipocalin in urine and cystatin C in blood serum was correlated with indicators of microalbuminuria, BMI, GFR and HOMA-IR. In groups 3 and 4, a negative average correlation between HOMA-IR and CKD (CKD-EPIcysC/cr) was established.

Conclusion. The conducted researches indicate an increase in the secretion of lipocalin-2 with urine, especially in people with CKD and a higher body mass index. It can be a significant predictor of albuminuria and is positively correlated with the level of cystatin C and HOMA-IR index. Rates of insulin resistance increased with progression of renal damage.

Key words: chronic kidney disease, obesity, lipocalin-2, cystatin C, insulin resistance.

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Н. В. Губіна, І. Г. Купновицька, Н. М. Романишин

ЦИСТАТИН С ТА ЛІПОКАЛІН-2 ЯК БІОМАРКЕРИ ПОЧАТКОВИХ ПОРУШЕНЬ ФУНКЦІЇ НИРОК У РАМКАХ НИРКОВО-МЕТАБОЛІЧНОГО КОНТИНУУМУ

Івано-Франківський національний медичний університет, Івано-Франківськ, Україна

Актуальність проблеми ураження нирок у пацієнтів з ожирінням зумовлена ростом частоти нефропатій, пов'язаних з метаболічними порушеннями.

Мета дослідження – оцінити зміни ліпокаліну-2 у сечі як раннього біомаркера порушення функції нирок на тлі ожиріння, його взаємозв'зок з цистатином С та показником інсулінорезистентності HOMA-IP у таких пацієнтів.

Ліпокалін-2 розглядається як ранній маркер тубулоінтестінального пошкодження нирок. Проведені дослідження свідчать про зростання секреції ліпокаліну-2 із сечею, особливо у осіб з хронічною хворобою нирок та вищим індексом маси тіла. Він може виступати значущим предиктором альбумінурії та позитивно корелює з рівнем цистатину С, індексом HOMA-IP. Показники інсулінорезистентності зростали у міру прогресування ураження нирок.

Ключові слова: хронічна хвороба нирок, ожиріння, ліпокалін-2, цистатин С, інсулінорезистентність.

Normal indicators of metabolism, renal function, and cardiovascular status reflect the interaction between metabolic risk factors, chronic kidney disease, and cardiovascular status, which have a significant impact on morbidity and mortality [1]. Obesity, type 2 diabetes mellitus (DM), cardiovascular disease (CVD) and chronic kidney disease (CKD) are recognized as some of the most significant public health problems today [2]. A large number of results of epidemiological and clinical studies confirm the existence of a close relationship between these conditions, as a result of which the term that unites them was defined – the cardio-renal-metabolic continuum [3]. This coexistence has various epidemiological, pathophysiological, and prognostic implications. Mechanisms of damage to the cardio-renal system caused by hyperglycaemia are better studied, but the development and progression of CKD and metabolic dysregulation remain problematic.

The background of the problem of kidney damage in patients with obesity is due to the increase in the frequency of nephropathies associated with metabolic disorders, their tendency to progress and the need to optimize early diagnosis [4]. Serum creatinine is an imperfect marker for determining kidney function, as its concentration does not change significantly until creatinine clearance falls below 70 mL/min/1.73 m^2. In addition, such factors as body weight, age, race, gender, inflammation, as well as taking certain drugs (in particular, H_2-histamine blockers) affect the creatinine level. Studies have shown that serum cystatin C is a more accurate predictor of kidney function compared to creatinine [5]. Cystatin C is an endogenous marker that is freely filtered in the glomeruli. Like other proteins with a low molecular weight, cystatin C is almost completely reabsorbed by the epithelial cells of the tubules and is subsequently catabolized, so it does not return to the bloodstream. In addition, it is not affected by inflammation, muscle mass compared to creatinine [6]. Another potential biomarker, neutrophil gelatinase-associated lipocalin (NGAL, lipocalin-2), is a part of the lipocalin family. It is also known as lipocalin-2 and is a small protein purified from neutrophil granules and is encoded by the lipocalin-2 gene on chromosome 9 [7]. According to some new hypotheses, the release of NGAL from the renal tubules occurs shortly after injury, preceding the rise in creatinine. In addition to separate researches that described NGAL together with other already known factors as an independent risk marker for CKD progression [8], F. Gharishvandi, F. Kazerouni et al. (2015) suggest that NGAL can be used as a biomarker of kidney disease and its severity [9]. However, at present, changes in cystatin C and lipocalin in patients with the initial stages of CKD and the presence of metabolic disorders, in particular, obesity, have been poorly studied. In turn, obesity is closely related to the development of systemic insulin resistance due to impaired utilization of glucose in skeletal muscles, which leads to compensatory hyperinsulinemia. Therefore, it is currently important to study the main mechanisms of the development and progression of obesity-related chronic kidney disease in order to develop new early strategies to prevent and slow down the progression of kidney damage in the future.

The purpose of the work is to evaluate changes in lipocalin-2 in urine as an early biomarker of renal dysfunction against the background of obesity, its relationship with cystatin C and HOMA-IR index in such patients.

Materials and methods. 300 patients with chronic kidney disease were examined, including 134 women and 166 men, who were hospitalized in the arterial hypertension department of the Communal non-commercial enterprise "Ivano-Frankivsk Regional Clinical Cardiology Centre of Ivano-Frankivsk Regional Council" and the urology and cardiology departments of the Communal non-commercial enterprise "Central City Clinical Hospital of Ivano-Frankivsk City Council" in Ivano-Frankivsk City (Ukraine). The average age of the examinees was (55.36±2.02) years for women and (47.45±2.66) years for men.

The body mass index was calculated according to the Quetelet formula (kg/m^2): BMI=body weight, kg(height), m^2.

The stage 1 of CKD was diagnosed in 140 patients (61 women and 79 men, whose average age was 46.43±3.77 years), and the stage 2 was diagnosed in 160 patients (76 women and 84 men, whose average age was 53 .07±2.61 years). The patients were divided into 4 groups: group 1 (70) – patients with stage 1 CKD and normal body weight, group 2 (72) – patients with stage 2 CKD and normal body weight; group 3 (70) – patients with stage 1 CKD and obesity, group 4 (88) – patients with stage 2 CKD and obesity. The control group consisted of 30 practically healthy individuals (13 women and 17 men), whose average age was 36.7±8.6 years.

Causes of CKD development are as follows infections of the upper parts of the urinary system in 11.8%, urolithiasis in 19.89%, previous glomerulonephritis with symptomatic renoparenchymatous arterial hypertension in 15.76%, abnormalities in the development of urinary reproductive system in 6.9%, essential arterial hypertension in 29.1% and coronary heart disease with heart failure in 18.89%. The average duration of CKD was 7.1 years. Exclusion criteria were diabetes mellitus, hypothalamic and endocrine obesity, acute myocardial infarction, congestive heart failure stage 3–4 according to NYHA, liver failure, stages 3–4–5 CKD.

All patients underwent general clinical examinations. Determination of albumin in daily urine was carried out by the turbometric method using the Microalbumin diagnostic kit (Germany) and was estimated in mg/day. Glomerular filtration rate was calculated according to the CKD-EPI formula based on the level of creatinine, cystatin C and their combination (CKD-EPIcysC/cr) (ml/min/1.73 m^2) using the calculator of the National Kidney Foundation of the USA http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). The level of cystatin C in blood serum (in healthy individuals – 0.79–2.15 mg/l) was studied by the enzyme immunoassay method using Human Cystatin C ELISA kit (Czech Republic) on the STAT FAX analyzer (No. 7898). The level of neutrophil gelatinase-associated lipocalin (urine-NGAL) (ng/ml) was determined by the 'sandwich' enzyme immunoassay method in urine (in healthy individuals – 0.16–10 ng/ml) using the HUMAN NGAL ELISA Kit (USA). To assess insulin resistance, the HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index was used, which was determined by the immunochemiluminescence method and calculated according to the formula:

HOMA-IR = fasting insulin (μU/ml) x fasting glucose (mmol/l) / 22.5 (reference values 0–2.7).

Determination of the level of glycosylated haemoglobin (HbA1c) was carried out by the spectrophotometric method (reagent Glycosylated haemoglobin, plastic silicates, Ukraine).

The research protocol was approved by the ethics commission of the State Higher Educational Institution "Ivano-Frankivsk National Medical University", Protocol No. 97/17 of 19 October 2017. All patients gave informed consent to participate in it. The research was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with the participation of a person as an object of research" of 1 October 2008, No. 900_005.

Statistical processing of the obtained results was carried out using the statistical analysis program Statistica 10.0. Arithmetic mean values (M) and standard deviation (SD) were calculated for quantitative traits when the data were normally distributed or median with lower and upper quartiles (Me [LQ; UQ] when the distribution was different from normal. For qualitative traits, the absolute frequency of manifestations was calculated characteristics (number of subjects), frequency of occurrence in % or 95% confidence interval (CI). The analysis of the data distribution was carried out using the Shapiro-Wilk and Kolmogorov-Smirnov test. Statistical analysis was carried out using non-parametric methods (Kruskal-Wallis test), since most of the features had data distribution other than normal. Spearman's rank correlation coefficient was used to assess correlations. Differences in results were considered statistically significant at $p<0.05$.

Results. According to the results of our research, the urinary excretion of lipocalin-2 in patients of all groups exceeded the indicators in healthy individuals, in particular, in patients of groups 1, 2, 3 and 4 by 1.5, 3.7, 3.1 and 5.6 times, respectively ($p_1<0.05$, $p_{2,3,4}<0.001$) (Table 1).

The growth of urinary excretion of NGAL was higher in patients of group 4 with a higher body mass index. Comparing u-NGAL indicators in patients with obesity, it was established that in patients with stage 2 CKD against the background of obesity, it was 1.8 times higher ($p<0.05$) than in patients with stage 2 CKD against the background of obesity. The level of daily microalbuminuria in patients of groups 1, 2, 3 and 4 exceeded the indicators in healthy individuals by 3.5, 4.2, 6.1, and 8.7 times, respectively ($p_{1,2,3,4}<0.001$). An increasing level of NGAL in urine was found to be a significant predictor of albuminuria, especially among patients of group 4.

The cystatin C level also exceeded the levels of healthy subjects in all groups, respectively, by 1.8, 2.7, 2.8 and 3.8 times (p1,2,3,4<0.001). In patients of group 4, the cystatin C level was 1.4 times higher than in patients of group 2, and 1.3 times higher than in patients of group 3 ($p>0.05$). The increase in serum cystatin C levels reflects the condition of glomerular filtration and the degree of renal function decline [10]. The GFR formula CKD-EPIcysC/cr indicates a 1.2-fold decrease in this indicator in patients of group 2 compared with group I, and in patients of group 4 compared with group 3 by 1.3 times ($p<0.001$), which confirms renal dysfunction despite normal creatinine values.

A positive mean correlation was found between NGAL and BMI in patients of groups 3 and 4 – r3=0.45, r4=0.58 (p3.4<0.05), between NGAL and microalbuminuria – r3=0.45, r3=0.48 (p3.4<0.05), between NGAL and cystatin C – r3=0.46, r4=0.68 (p3.4<0.05). In patients of group 4, a direct average correlation was found between daily albuminuria and BMI – r=0.56, $p<0.05$, indicating a deterioration in the functional state of the kidneys against the background of obesity. In groups 3 and 4, a negative mean correlation was found between NGAL and GFR (CKD-EPIcysC/cr) – r3= -0.56, r4= -0.58 (p3.4<0.05), indicating impaired renal function even in the initial stages of CKD.

According to Belinda Spoto, Anna Pisano, Carmine Zoccali (2016), insulin resistance is present in the early stages of CKD and increases with the progression of

Table 1

Characteristics of laboratory indicators in examined patients

Indicators	Healthy, n=30	Group 1, n=70	Group 2, n=72	Group 3, n=70	Group 4, n=88
BMI, kg/m^2	21.67 [21.00; 22.60]	24.94 [21.70; 25.00]	22.13 [21.40; 23.20]	34.03 [32.60; 35.50]	37.52 [36.10; 38.60]
GFR, ml/min/1.73 m^2 CKD-EPIcysC/cr	109.62 [101.00; 118.00]	94.27 * [90.00; 99.00]	78.03* º [76.00; 81.00]	94.04 * [90.40; 99.00]	70.54 *Δ [62.00; 78.00]
Cystatin C, mg/l	0.78 [0.70; 0.81]	1.44 * [1.20; 1.80]	2.11 *º [1.99; 2.30]	2.22 *▫ [2.00; 2.60]	2.97 *× [2.87; 3.10]
Creatinine, mcmol/l	78. 27 [76.00; 87.20]	83. 82 [79.80; 88.00]	94. 60 * [88.00; 100.00]	103. 97 *▫ [90.50; 116.00]	106. 19 * [96.00; 116.10]
Albuminuria, mg/ day	19.50 [18.00; 22.00]	68.21 * [49.00; 84.00]	81.60 *º [76.50; 88.00]	118.55 * [100.00; 134.00]	169.72 *Δ× [156.00; 189.00]
General cholesterol, mmol/l	4.41 [4.10; 4.80]	6.33 * [5.50; 7.30]	6.31 * [5.50; 7.10]	6.49 * [5.40; 7.80]	6.80 * [5.70; 7.88]
NGAL, ng/ml	4.26 [3.40; 4.99]	6.43 * [4.88; 7.88]	15.93 *º [13.88; 17.89]	13.59 *▫ [12.00; 16.20]	23.95 *Δ× [22.00; 27.00]
Glucose, mmol/l	4.4 [4.20; 4.50]	4.6 [4.40; 4.80]	5.0 [4.80; 5.10]	5.0 [4.80; 5.30]	5.8 [5.50; 6.00]
HOMA-IR	1.44 [1.43; 1.50]	1.44 [1.42; 1.53]	1.56 [1.54; 1.67]	4.3 *▫ [3.60; 4.87]	5.68 *Δ× [5.10; 6.10]
HbA1c, %	4.0 [4.00; 4.10]	4.2 [4.00; 4.50]	4.6 [4.50; 4.88]	4.8 [4.50; 4.90]	5.6 *Δ× [5.40; 5.80]

***** – statistically significant difference in indicators compared to the healthy group

° – statistically significant difference in indicators comparing groups 1 and 2

Δ – statistically significant difference in indicators comparing groups 3 and 4

▫ – statistically significant difference in indicators comparing groups 1 and 3

× – statistically significant difference in indicators comparing groups 2 and 4

CKD [11]. In patients of group 1, the HOMA-IR index was practically no different from that of healthy subjects, in patients of group 2 it increased slightly by 1.1 times, and in patients of group 3 it was 2.9 times higher than in healthy subjects and patients of group 1 ($p<0.001$). In patients of group 4, the HOMA-IR index was 3.9 times higher than in healthy subjects ($p<0.001$), 3.6 times higher than in patients of group 2 ($p<0.001$), and 1.32 times higher than in patients of group 3 ($p<0.05$). Blood glucose levels in patients of all groups did not differ significantly and did not exceed the normal range. The level of glycated haemoglobin in groups 1, 2 and 3 did not differ from the level in healthy subjects, and in patients of group 4 it was 1.4 times higher than in healthy subjects ($p<0.05$), 1.2 times higher than in patients of groups 2 and 3 ($p<0.05$). Our data are in line with the studies of H. de Boer, and Rajnish Mehrotra (2014), who proved that induction of insulin resistance in podocytes leads to glomerulosclerosis in animal models, and insulin resistance is associated with albuminuria and the development of CKD in human studies [12].

Analysis of the correlations between the indicators revealed a positive mean correlation between HOMA-IR and cystatin C in patients of group 4 Ian $r=0.4$ ($p<0.05$) (Fig. 1), between HOMA-IR and NGAL in patients of group 4 Ian $r=0.35$ ($p<0.05$), between HOMA-IR and MAU in patients of groups 3 and 4 – $r3=0.35$, $r4=0.33$ ($p3, 4<0.05$), between HOMA-IR and BMI in patients of group 4 – $r=0.45$ ($p<0.05$), between HOMA-IR and HbA1c in patients of group 4 – $r=0.62$ ($p<0.001$) (Fig. 2), between HOMA-IR and glucose level in patients of groups 3 and 4 – $r3=0.54$, $r4=0.73$ ($p3.4<0.001$). Our results are also in line with J. Bae, S. Seo, K. Hur, J. Kim, M. Lee, M. Lee et al. (2013), who proved that a positive relationship between HbA1c and HOMA-IR indicates the presence of chronic mild hyperglycaemia and decreased insulin sensitivity even in the absence of overt diabetes in people with mild to moderate CKD [13].

In groups 3 and 4, a negative mean correlation between HOMA-IR and GFR (CKD-EPIcysC/cr) was found – $r3=-0.36$, $r4=-0.46$ ($p3.4<0.05$). De S. Cosmo, C. Menzaghi, S. Prudente (2013) found that hyperinsulinemia affects renal function by inducing glomerular hyperfiltration, endothelial dysfunction and subsequently leads to a faster decline in renal function compared to patients who are insulin sensitive [14].

Discussion. Obesity is an important cause of microvascular dysfunction, which may precede nephropathy [15]. S. Zoungas, H. Arima, H.C. Gerstein, R.A. Hayward et al. (2017) also analyzed the impact of insulin resistance (IR) and obesity on chronic kidney disease [16]. The relationship between hyperglycaemia and renal dysfunction is bidirectional and can be seen as a vicious circle. Experimental

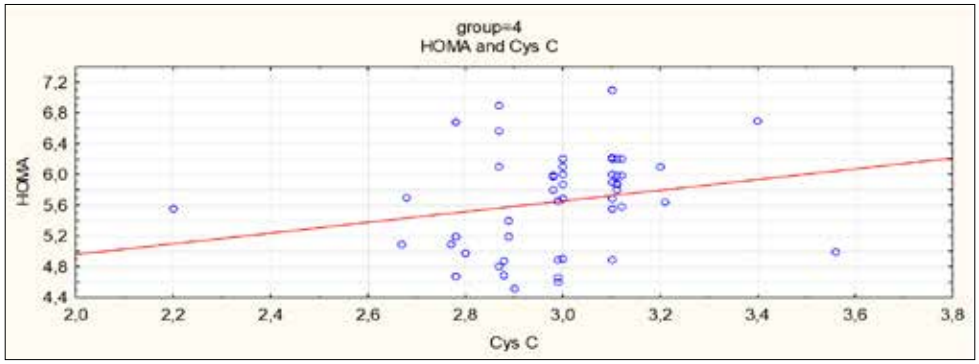

Fig. 1. Correlation between HOMA-IR and cystatin C in patients of group 4

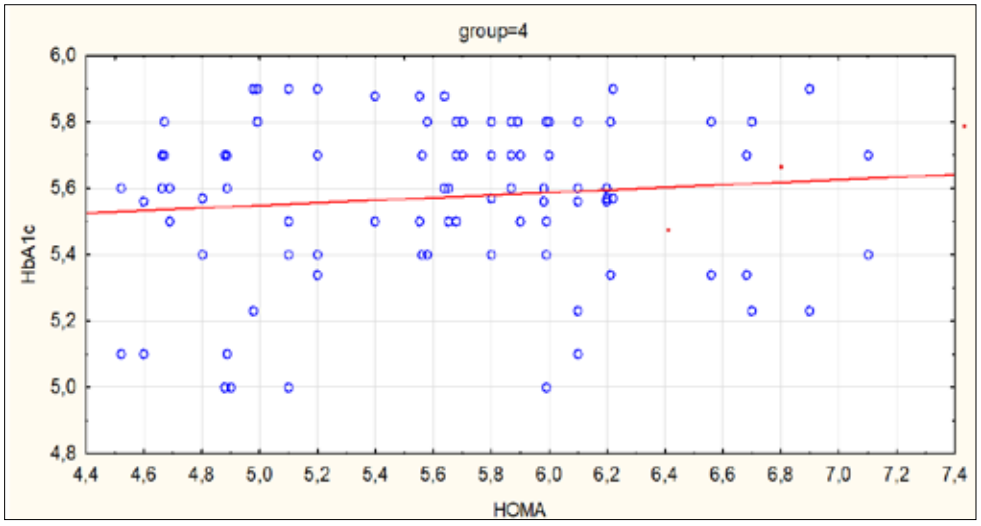

Fig. 2. Correlation between NOMA-IR and glycosylated haemoglobin in patients of group 4

evidence suggests that hyperglycemia can cause microvascular damage to the tubulointerstitial apparatus of the kidneys [17].

It is known that a significant part of cystatin C is synthesized by adipocytes of subcutaneous and visceral adipose tissue. Obesity is associated with a significant increase in cystatin production by adipocytes [18]. The possibility of detecting NGAL (u-NGAL) in urine in people with kidney disease has led to the evaluation of lipocalin-2 as an early non-invasive biomarker for acute and chronic kidney injury in humans in numerous studies, and has proven its role as one of the most promising early biomarkers for the diagnosis of CKD and associated metabolic disorders [19].

Adipocytokine, lipocalin-2, plays a key role in the regulation of body fat mass and insulin resistance, as well as regulates energy, glucose and lipid metabolism [20]. The role of NGAL in the pathogenesis of obesity and renal dysfunction is not well understood. Both preclinical and clinical studies have shown that lipocalin may play a role in the pathogenesis of obesity and the ability of liver and muscle cells to use insulin [21]. A study by S.B. Ascher et al. (2022) found that NGAL plays a dominant diagnostic role compared to cystatin C and creatinine in detecting renal deterioration in the early stages of CKD and in predicting its progression [22]. Our results indicate the presence of renal tubular damage, as evidenced by elevated levels of u-NGAL and cystatin C among patients with CKD, obesity, and insulin resistance. According to Sarah J. Schrauben, Christopher Jepson, Jesse Y. Hsu et al. (2019), insulin mediates renal function mainly at the tubular level, where specific insulin binding is highest [23]. There is evidence in the available literature that insulin acts in the proximal tubule, and hyperinsulinemia leads to a decrease in nitric oxide, an increase in transforming growth factor-β1 and insulin-like growth factor-1, and endothelin-1 production, which leads to increased oxidative stress [24]. These mechanisms are likely to explain the increase in urinary NGAL and serum cystatin C found in the CKD and obese groups, which also had elevated levels of glucose, HOMA and glycated hemoglobin compared to the control group.

Conclusion. Thus, lipocalin-2, as one of the adipocytokines, plays a key role in the regulation of insulin resistance, glucose metabolism, and is also considered an early marker of tubulointerstitial renal injury. Studies have shown an increase in urinary lipocalin-2 secretion, especially in patients with a higher body mass index (BMI). It can be a significant predictor of albuminuria and positively correlates with cystatin C levels and the HOMA-IR index. Insulin resistance was higher in patients with CKD and obesity and increased with the progression of renal damage.

Prospects for further development. Study of the relationship between the components of the metabolic syndrome, in particular, obesity, insulin resistance with the progression of CKD, cardiovascular events and death among a cohort of patients with CKD without diabetes and study of the effectiveness of preventive therapy in preventing the progression of CKD against the background of obesity.

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Електронна адреса для листування natali.gubina1974@gmail.com