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CYSTATIN C AND COLLAGEN TYPE IV IN CHRONIC KIDNEY DISEASE DIAGNOSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSRTACT

Goal. To compare markers of kidney damage – glomerular filtration rate (GFR), calculated by creatinine and cystatin C, urinary excretion of cystatin C, type IV collagen and albumin in patients with type 2 diabetes mellitus (DM2) with normal and moderately reduced kidney function.

Materials and methods. 56 patients with DM2, aged 43 to 70 years, and 16 people without diabetes and chronic kidney disease (CKD), aged 40-72 years, were examined. GFR was determined by formulas based on the level of creatinine (CKD-EPIcreat), cystatin C (CKD-EPIcys) or both markers (CKD-EPIcreat-cys). The concentration of cystatin C in blood serum and urine was determined by immunoturbidimetric method, urinary albumin excretion (EAM) and type IV collagen excretion by enzyme immunoassay. The composite body composition was studied in 24 patients using dual-energy X-ray absorptiometry.

Results. In patients with DM, the level of cystatin C in the blood serum positively correlated with age (r=0.37), GFR according to CKD-EPIcreat (r=-0.43) and the percentage of adipose tissue (r=0.55). There was a positive correlation between the GFR calculated by CKD-EPIcys and CKD-EPIcreat (r=0.48). In multivariate regression analysis, the percentage of adipose tissue influenced the GFR calculated by CKD-EPIcys and CKD-EPIcreat-cys. Urinary excretion of cystatin C was not It is associated with the level of cystatin C in serum, GFR and EAM. The excretion of type IV collagen was increased in patients with reduced GFR compared to patients without reduction (p=0.002). The content of type IV collagen in urine correlated with GFR and EAM (r=-0.28 and r=0.47).

Conclusion. Measuring the level of cystatin C in blood serum with the calculation of GFR by CKD-EPIcys and CKD-EPIcreat-cys, in addition to CKD-EPIcreat, increases the accuracy of the diagnosis of CKD in patients with DM2. Obesity and, in particular, adipose tissue mass affect the assessment of GFR based on cystatin C. An increase in urinary excretion of type IV collagen, but not cystatin C, is associated with a decrease in GFR and an increase in EAM in these patients.

Keywords: type 2 diabetes mellitus; chronic kidney disease; glomerular filtration rate; cystatin C; type IV collagen

INTRODUCTION

Early diagnosis of chronic kidney disease (CKD) is one of the most important tasks in the management of patients with diabetes mellitus (DM). National and foreign expert groups It is recommended to determine urinary albumin excretion (EAM) and glomerular filtration rate (GFR) as mandatory tests for the diagnosis of CKD with DM. The informativeness of these tests has known limitations. The diagnostic value of albuminuria limits its variability, dependence on diet and exercise, the presence of urinary tract infection, fever, ketoacidosis. Sources of errors in determining GFR by creatinine level may be non-standard body sizes, nutritional features (high-protein diet, creatine-containing dietary supplements), changes in muscle tissue, taking medications (trimethoprim, cimetidine, fenofibrate), analytical errors caused by the effects of ketones, bilirubin and other molecules. In this regard, the search continues for new markers that can improve the accuracy of the diagnosis of CKD in patients with DM.

As an endogenous marker for determining GFR proposed cystatin C, a low molecular weight protein with a molecular weight of 13.4 kDa. Cystatin C it passes freely through the glomerular filter and is completely reabsorbed and catalyzed by tubular epithelial cells. An increase in the level of cystatin C in blood serum is observed with a decrease in renal filtration function, while an increase in its urinary excretion indicates dysfunction of proximal tubule cells. In 2012, experts from KDIGO (Kidney Disease Improving Global Outcomes) recommended using cystatin C as an additional method to creatinine for determining renal filtration function for improving the accuracy of the GFR assessment. The preference for evaluating GFR by creatinine and/or cystatin C levels in different categories of patients continues to be discussed. It has been shown that the level of cystatin C in the blood is influenced not only by kidney function, but also by the presence of obesity. The possibilities of using GFR calculations based on the level of cystatin C in obese patients and type 2 diabetes mellitus (DM2) are being studied. Determination of urinary excretion of type IV collagen is proposed as a test for assessing fibrogenesis in the kidneys. Type IV collagen is the main component of the basement membranes of the glomeruli and tubules, as well as the mesangial matrix of the renal glomeruli.

Accumulation of type IV collagen in the basement membranes and mesangium is one of the earliest morphological signs of diabetic nephropathy that occurs in some patients before the increase in EAM.

The aim of the study was to compare various markers of kidney damage: GFR indicators calculated by creatinine and cystatin C, urinary excretion of cystatin C, type IV collagen and albumin in patients with DM2 with normal and moderately reduced filtration function.

MATERIALS AND METHODS

56 patients with DM2 were examined, 13 men and 43 women, from 43 to 70 years old (median 62 years), with a disease duration from the moment of diagnosis of 6 up to 36 years (median 13 years). The body mass index (BMI) ranged from 21.8 to 39.8 kg/m2 (median – 32 kg/m2); overweight was recorded in 12 people, obesity – in 37. All patients included in the study received insulin therapy: basal insulin – 14 people, combined insulins – 8, basic bolus insulin therapy – 34. In addition to insulin 31 patients took metformin, 2 – sulfonylureas, 8 – a combination of metformin and sulfonylureas. The level of glycated hemoglobin A1c (HbA1c) was in the range of 5.9–11.4% (median 8%). All patients had arterial hypertension and received angiotensin-converting enzyme inhibitors or receptor antagonists angiotensin II as monotherapy or in combination with other antihypertensive agents. The study did not include patients with primary kidney pathology of nondiabetic genesis, infection urinary tract, nephrotic syndrome, CKD stages 4-5, autoimmune and chronic inflammatory diseases.

Study of albumin and collagen concentrations Type IV in the morning portion of urine was carried out by enzyme immunoassay using a BioRad 680 reader (BioRad, USA) and Zemfira software. The result of the determination resulted in the amount of creatinine excreted. The albumin concentration was determined using a test-Albumin ELISA systems from Immundiagnostik (Germany). Based on the albumin/creatinine ratio, 43 of the examined patients had normal EAM, 13 had elevated EAM. Determination of the concentration of type IV collagen was carried out using sets of Urinal Collagen IV EIA by DAIICHI FINE CHEMICAL CO.LTD (Japan). The concentration of cystatin C in urine was determined by the immunoturbidimetric method on an analyzer Abbott Architect c8000 with reagent kits Cystatin C-AT of Alfresa Pharma Corporation (Japan). Considering that the introduction of a correction for creatinine dependent on tubular reabsorption and secretion may worsen the diagnostic value of the study of cystatin C excretion, the concentration of cystatin C in urine was evaluated without conversion to creatinine.

The control group for laboratory studies consisted of 16 people, 9 men and 7 women, aged 40 to 72 years (median – 66 years), without diabetes, with normoalbuminuria

and normal creatinine levels in the blood. In 24 patients, including 17 with obesity and 7 without obesity, a study of the composite composition of the body was performed using dual-energy X-ray absorptiometry on the Lunar Prodigy apparatus (USA), using the Total Body Composition program. The research protocol has been approved by the local ethics committee. All patients gave written informed consent to participate in the study. Statistical processing was carried out using the STATISTICA 10 program (StatSoft, Inc, 2011, USA). Considering that the distribution of most of the studied features was different from normal, nonparametric statistics methods were used. Intergroup differences were assessed using the criterion Mann-Whitney and ANOVA Kraskel-Wallis. The characteristics were studied using Spearman's rank correlation analysis, multivariate step-by-step regression analysis. Variables with a distribution other than normal were subjected to logarithm before being included in multivariate models. The critical level of significance when testing statistical hypotheses was assumed to be 0.05. Data presented as medians, 25th, 75th percentiles.

RESULTS

The concentration of cystatin C in the blood serum of the examined DM patients varied from 0.48 to 1.98 mg/l, averaging 0.96 (0.82; 1.11) mg/l, in the control group – from 0.74 to 1.11 mg/l, on average 0.96 (0.9; 1.08) mg/l. The level of cystatin C in patients DM was positively correlated with creatinine levels in blood (r=0.47, p=0.0003) and negatively – with GFR calculated by CKD-EPIcreat (r=-0.43, p=0.0009). The level of cystatin C was not correlated with EAM (r=-0.03, p=0.83). Obese patients with DM2 had a higher level of cystatin C in the blood compared to other patients: 0.98 (0.9; 1.13) and 0.84 (0.76; 0.99) mg/l, respectively, p =0.04. There was a positive relationship between the content of cystatin C and the age of patients (r=0.37, p=0.005). The content of cystatin C was not associated with the level of HbA1c (r=-0.05, p=0.71), but showed a positive relationship with the duration of DM from the moment of diagnosis (r=0.32, p=0.02). GFR values calculated based on the level of cystatin C in patients with DM were on average 9 ml/min /1.73 m2 higher compared to the values GFR calculated by creatinine. In the control room the group, on the contrary, showed higher GFR values when calculating creatinine. The results obtained taking into account both parameters (formula CKD-EPIcreat-cys), expected to occupy an intermediate position.

In patients with DM, there was a correlation of average strength (r=0.48, p=0.0002) between GFR values calculated using the formulas CKD-EPI creat and CKD-EPI cis. Closer correlations were observed between GFR for CKD-EPI creat and CKD-EPI meat-cs (r=0.81, p<0.0001), as well as between GFR for CKD-Epicus and GFR for

CKD-EPI creat-cis (r=0.88, p<0.0001). Differences in GFR indicators defined by according to the formulas CKD-EPI creat and CKD-EPI cis, in the range 11-19 ml/min/1.73 m2 were recorded in 14 patients, >20 ml/min/1.73 m2 – in 12, in the rest the difference in indicators did not exceed 10 ml/min/ 1.73 m2. In the control, differences in GFR indicators for CKD-EPI creat and CKD-EPI gas from 11 to 19 ml/min/ 1.73 m2 were detected in 5 people, in 5 more cases the difference exceeded 20 ml/min/1.73 m2. In 10 patients, GFR indicators calculated according to the formulas CKD-EPI creat and CKD-EPI clip, gave the basis in different ways to diagnose CKD: in six (including five with normal EAM) out of 16 patients with GFR by CKD-EPI creat within 30-59 ml/min/1.73 m2, the GFR calculated by CKD-Epicus was >60 ml/min/1.73 m2; in two cases, GFR <60 ml/min/1.73 m2 is determined only by the formula CKD-EPI clip.

As can be seen from, patients with normal or overweight (BMI <30 kg/m2) in comparison with obese patients had significantly higher GFR values calculated by cystatin C, but not by creatinine. The GFR index according to CKD-Epi correlated with BMI (r=-0.3, p=0.02).

The relationship of creatinine and cystatin C levels, as well as GFR indicators calculated on the basis of their concentrations, with the parameters of the composite composition of the body are presented in. The correlation analysis revealed positive relationships between the concentration of cystatin C, the mass of adipose tissue and its proportion in the body, as well as inverse correlations between the GFR calculated by CKD-Epicus and the specified parameters of the composite composition. In multivariate regression analysis, the percentage of adipose tissue in the body turned out to be independent of- the speaker of the GFR calculated by CKD-EPIcys (β=-0.62, R2=0,43, p=0,006). The proportion of adipose tissue retained its influence on the GFR index when using the formula CKD-EPIcreat-cys (β=-0,54, R2=0,32, p=0,03).The fat content did not have a significant effect on the GFR according to CKD-EPI creat.

Urinary excretion of cystatin C in the majority of the examined patients (n=40) was at the level of 0.1 ng/ml, which corresponded to the lower threshold of sensitivity of the method. The concentration of cystatin C >0.1 ng/ml was detected in 19 patients. In the control group, the concentration of cystatin C exceeded >0.1 ng/ml in two cases, low values were detected in the remaining samples indicator (0.1 ng/ml). Significant differences in cystatin C excretion between the examined patients there were no patients with DM2 and the control group (p=0.33). Patients with GFR according to CKD-EPIcreat-cys in the range 30-59 ml/min/1.73 m2 did not differ from patients with GFR >60 ml/min/1.73 m2 by urinary excretion of cystatin (p=0.5). There were

no differences in the concentration of cystatin C in urine in patients with normal and elevated EAM (p=0.47). In the rank correlation analysis, there was no relationship between the level of cystatin C in the blood and in the urine. Weak inverse correlations of the concentration of cystatin in urine with the mass of fat and muscle ("non-fat") tissue, as well as a direct correlation with the volume has not reached the degree of statistical significance.

Average urinary excretion of collagen Type IV patients with DM did not differ from those in the control group. At the same time, high excretion values were recorded in 12 patients with DM (>0.51 mcg/mmol creatinine), not observed in the control. High excretion of type IV collagen was characteristic of patients with GFR according to CKD-EPIcreat-cys in a range of 30-59 ml/min/1.73 m2 (Fig. 1). The excretion of type IV collagen in patients with decreased GFR exceeded the indicator in the control (p=0.03) and in patients with GFR>60 ml/min/1.73 m2 (p=0.003). Surveyed Patients with elevated EAM also had significantly higher values of type IV collagen excretion compared to patients with normal EAM: 0.34 (0.24; 0.52) and 0.16 (0.07; 0.26) mcg/mmol of creatinine, respectively, p=0.002. At the same time, increased individual the values of type IV collagen excretion were recorded in four patients with GFR >60 ml/min/1.73 m2 and in seven patients with normoalbuminuria.

Urinary excretion of type IV collagen positively correlated with albuminuria, cystatin C levels in blood and negative – with GFR calculated by creatinine and/or cystatin C. There were no significant correlations between the content of type IV collagen in urine and age, BMI, indicators of body composite composition, duration of diabetes and HbA1c level. In a multi- factor step-by-step regression analysis, an increase in the excretion of type IV collagen was facilitated by an increase in EAM and a decrease in GFR according to CKD-EPIcreat-cys (β=0.317 and β=-0.38, respectively, R2=0.27, p<0.0001).

DISCUSSION

A decrease in GFR in patients with DM2 is often observed in the absence of increased albuminuria and, consequently, is a decisive method for the diagnosis of CKD. Given the limited availability of "direct" methods for determining GFR, as well as methodological limitations that arise when determining GFR by creatinine, attempts are being made to find alternative ways to assess renal filtration function. It is shown that the GFR estimation formulas based on cystatin C give less biased with respect to the reference According to the isotopic method (51Cr-EDTA), the GFR values are compared with the MDRD formula [7]. In our study, a comparison of GFR indicators calculated according to the formulas recommended by KDIGO experts was carried out

CKD-EPIcreat (2009) and CKD-EPIcys (2012), in patients DM2 with normal and moderately reduced function kidneys. A correlation of average strength is established between the values of GFR calculated by these formulas (r=0,48). At the same time, 10 out of 56 examined patients had GFR indicators calculated according to CKD-EPIcreat formulas and CKD-EPIcys, gave reason to diagnose the presence or severity of CKD differently. Experts KDIGO recommends examining the level of cystatin With in the blood with the calculation of GFR by CKD-EPIcys, CKD-EPIcreat-cys, in patients with creatinine GFR 45-59 ml/min/1.73 m^2, with no other signs renal damage. The data we received they also indicate the feasibility of calculating GFR based on the determination of creatinine and cystatin C (CKD-EPIcreat-cys formula) in patients with DM2 for verification Stage 3 CKD.

The level of cystatin C, as well as blood creatinine, is characterized by low intraindividual variability [14]. The disadvantage of determining GFR by cistatin C in comparison with creatinine is lower availability and higher cost of analysis [3]. When interpreting GFR indicators calculated by cystatin C, their dependence should be taken into account depends on age and body weight. An increase in the concentration of cystatin C in adults with increasing age and degree of obesity has been demonstrated in a large-bullet study of NHANES III (Third National
Health and Nutrition Examination Survey) [6]. Excess adipose tissue in obesity may be a source of an additional amount of cystatin C in the bloodstream. It has been shown that the expression level of cystatin C in adipocytes of subcutaneous tissue and omentum of a person, on average, it is 2 times higher than in other tissues. The presence of obesity is associated with a two– to three-fold increase in the secretion of cystatin with adipocytes [15]. In persons with abdominal obesity and insulin resistance- By stent, an increase in cystatin C is associatedwith the risk of developing DM2 [16]. Our study of the composite composition of the body showed that the mass of adipose tissue has a direct effect on the level of cystatin C and a reverse effect on the GFR calculated according to CKD-EPIcys. At the same time, the fat content did not have a significant effect on the GFR index according to CKD-EPIcreat. Informativeness of the use of
different methods for assessing GFR based on cystatin C, in persons with morbid obesity deserves special studies.

With the level of cystatin C in blood and urine in patients with DM2. Since normally cystatin C is completely reabsorbed in the proximal tubules, and its channel secretion has not been established, the detection of significant amounts of cystatin C in urine is considered as a marker of impaired reabsorption and tubular proteinuria. High concentrations of cystatin C in the urine, detected by us in some patients, may indicate

the presence of dysfunction (damage) of the epithelial cells of the proximal tubules. The study showed an increase in mo-increased excretion of type IV collagen in DM patients with reduced renal filtration function. Value collagen excretion was inversely correlated with GFR and directly with albuminuria. Previously, the relationship between the excretion of type IV collagen, GFR and proteinuria was revealed in patients with CKD of nondiabetic genesis. Increased excretion of type IV collagen is considered
as a sign of kidney fibrosis. In db/db mice (DM2 model), the relationship between the increase in
urinary excretion of type IV collagen and increased the volume of the glomerular mesangium. In patients with DM2 the excretion of type IV collagen correlated with its expression in the kidneys, reflecting the degree of expansion of the glomerular mesangium and the severity of tubulointerstitial changes. Increased excretion of type IV collagen was detected by us in 7 out of 43 patients with normal EAM and in four of 40 patients with GFR>60 ml/min/1.73 m2. It is possible that the urinary excretion of type IV collagen is a more sensitive test in the diagnosis of CKD with DM2 compared with the study of albuminuria. The results of an 8-year study conducted in Japan showed that increased excretion of collagen IV type in patients with DM2a, having normal ormicroaluminuria, is associated with a faster rate reduction of GFR.
The research we have carried out has obvious limitations. We did not perform a "direct" measurement GFR using exogenous filtration markers. Probably, additional information for judging the informativeness of the study of cystatin C and type IV collagen could be provided by lifetime morphological studies of the kidneys. At the same time, in this work, the comparison of GFR indicators calculated by the level of creatinine and cystatin C with urinary excretion of cystatin, type IV collagen and albumin was carried out for the first time in patients with DM2 with initial and moderate signs of CKD, the relationship of these markers with the composite composition of the body was analyzed. The data obtained indicate that the determinationof cystatin C in the blood with the calculation of GFR by cystatin C, the study of urinary excretion of cystatin C and type IV collagen, allow us to detail the severity of kidney damage in patients with DM2, taking into account the state of glomerular filtration, tubular reabsorption and the intensity of fibrogenesis.

CONCLUSION

Determination of the level of cystatin C in the blood serum with the calculation of GFR by the formulas CKD-EPIcys (2012) and CKD-EPIcreat-cys (2012), in addition to the calculation of GFR by creatinine (CKD-EPIcreat, 2009), increases the reliability of the

diagnosis of CKD in patients with DM2. Study Cystatin C is advisable in situations where GFR <60 ml/min/1.73 m2 is detected by CKD-EPIcreat in the absence of other signs of kidney damage. Cytotine C may be more accurate than creatinine as a marker of filtration function in DM patients with skeletal muscle diseases, in bodybuilders, taking creatine-containing dietary supplements, vegetarians, pregnant women. Establishing the informativeness of cystatin C in these groups of patients with diabetes is the task of future studies.

When interpreting the indicators of cystatin C in the blood and GFR calculated by the level of cystatin C, the effect of obesity on these indicators should be taken into account: an increase in adipose tissue mass correlates with an increase in the level of cystatin C in the blood and a decrease in GFR by CKD-Epicus. Regardless of the level of cystatin C in the blood, in some patients with DM2, cystatin C is detected in urine in significant amounts (>0.1 ng/ml), which, apparently, indicates the presence of dysfunction of the proximal tubules. The development of kidney damage in patients with DM2 character- it is characterized by an increase in urinary excretion of type IV collagen. The content of type IV collagen in urine is inversely correlated with GFR and directly correlates with albuminuria.

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