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Method of Using Cystatin C as A Predictor of Early Diagnostics of Diabetic Nephropathy

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ABSTRACT

The aim is to evaluate the possibility: The aim of the current study is the feasibility of using cystatin C level and glomerular filtration rate calculated using CKD-EPI$_{cys}$ and CKD-EPIcreat-$_{cys}$ formulas in the early diagnosis of diabetic kidney impairment in women with type 1 diabetes in the prep stage and in the first three months of in pregnant women.

Materials and research methods:The study sample consists of 47 women with type 1 diabetes, of whom 25 are pregnant and 22 are planning to become pregnant. For all patients, the level of cystatin C was determined, and the glomerular filtration rate was calculated using the methods of different test formulas (Rehberg, CKD-EPI$_{cr}$, CKD-EPI$_{cys}$, CKD-EPI$_{cr-cys}$), the dosage and regimen of insulin therapy were adjusted, and the training was conducted in a school diabetes.

Results: The results of the study showed that there is a difference between groups of pregnant women and those planning to become pregnant in the level of glycated hemoglobin (p = 0.001), the percentage of creatinine in the blood (p = 0.001), and the glomerular filtration rate calculated on the basis of the Rehberg test (p = 0.017). The formulas were CKD-EPI$_{cr}$ (p = 0.005) and CKD-EPI$_{cr-cys}$ (p = 0.046), and were comparable for urine creatinine, cystatin C, glomerular filtration rate determined by the CKD-EPI$_{cys}$ formula and based on daily protein loss. In the majority of pregnant women, when determining the glomerular filtration rate using the CKD-EPI$_{cr}$ formula, stage C1 was detected (87.5%) and only 12.5% was stage C2, which differs statistically significantly from the group of patients planning pregnancy, as the percentage of patients who Experienced by comparable C1 and C2 low glomerular filtration rate stages (p = 0.002). When regulating the glomerular filtration rate according to the CKD-EP$_{cys}$ formula, most pregnant women also have stage C1, while most women who plan to become pregnant have stage C2. Phase C3a was generated in both groups only when calculating the glomerular filtration rate using the CKD-EPI$_{cys}$ formula. When performing the glomerular filtration rate according to the Reberg test, most women from both groups were classified as stage C1, and the percentage of women with stages C1 and C2 in groups planning pregnancy and pregnant women did not differ significantly.

Key words: chronic kidney disease; diabetes mellitus; cystatin C; glomerular filtration rate; diabetic nephropathy; pregnancy, Nephropathy.

INTRODUCTION

It is usually used to identify non-invasive early signs of diabetic kidney impairment and to

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introduce them into clinical practice, in addition to giving preventive treatment to the kidneys in a timely manner to avoid these diseases in pregnant women, and it is considered an urgent and important task to improve the quality of life of diabetics, and reduce disability and mortality in women pregnant.

Every day the number of women and men with chronic diabetic kidney disease (CKD) increases worldwide. Chronic kidney disease is associated with a higher risk of cardiovascular disease, early disability, and death. The severity of chronic diabetic kidney disease is determined by the level of low glomerular filtration rate (GFR). Modern formulas to calculate GFR based on serum creatinine levels give errors, therefore, it is imperative to search for new scientific methods for assessing and determining GFR. A number of studies have shown the effectiveness of determination of cystatin C in the blood serum as a more sensitive predictor of low SFR for early detection of diabetic kidney disease especially in pregnant women. The timely detection of diabetic nephropathy and the appointment of treatment (protection of the kidneys and prevention of heart disease) is an important task in reducing the risk of cardiovascular disease and mortality. The review looks at the possibilities of using cystatin C as a marker of decreased kidney function, the diagnosis of cardiovascular disease and the development of preeclampsia.

Cystatin C and Cardiovascular Diseases: Reduced glomerular filtration rate is an important independent risk factor for the development and progression of cardiovascular disease and cardiovascular mortality. For the first time, an association between serum cystatin C and the development of heart failure (HF) in the general population was reported by M.J. Sarnak et al. Based on cardiovascular health study materials (Kiyosue A, 2010; Sarnak M.J. 2005). In patients with acute myocardial infarction, the concentration of cystatin C in the blood plasma was significantly higher than in patients with stable or unstable angina pectoris. In addition, after further observation for 6 months, the development of cardiovascular complications was associated with higher plasma levels of cystatin C. It is also noted that in elderly patients, regardless of the presence or absence of CKD, cystatin C is a biomarker for increased risk. Incidence of cardiovascular disease and reverses severity of coronary heart disease (Monteiro. J. Fd, 2012, Ix JH, 2006). Separate studies have shown a direct link between cystatin C and arterial hypertension. In patients with coronary artery disease, a linear relationship was found between cystatin C levels and systolic blood pressure values even in patients with normal kidney function. The relationship between serum cystatin C, myocardial hypertrophy, and left ventricular diastolic dysfunction was also determined. Cystatin C and the pathology of pregnancy The high level of cystatin C mRNA expression in the appendicular trophoblast cells in the basal region indicates the role of cystatin C in the regulation of protease activity during the placenta. The expression and secretion of cystatin C in the placenta may be associated with an increase in the maternal cystatin C level observed in preeclampsia (Christensen K.2007). Thus, in the ScoPE study, which included 47 pregnant women, it was found that in women with normal body mass index, the risk of preeclampsia correlated with a higher level of cystatin C at 14-16 weeks of pregnancy (Vieira M.C. 2017). In the study n. Franchini et al (Vieira M,C, 2017) proposed a mathematical model for pregnancy outcomes based on the concentration of cystatin C in the mother's blood. A high level of cystatin C has been shown to be an indication of the development of preeclampsia, regardless of the presence of other risk factors in pregnant women, such as obesity, maternal age, diabetes, kidney disease, etc. Preeclampsia increases 12 times with higher cystatin C values in the

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first trimester (fourth trimester) compared to lower cystatin C values (first trimester) (Franceschini N, 2008). Cystatin C ion diseases that in patients with malignancies correlate with serum cystatin C level with disease progression, and not only with glomerular filtration rate (Kos J, 1998). An increase in its content was found in blood serum and in tumor tissue in patients with rectal cancer (Yonida K, 2009) , and non-Hodgkin's lymphoma B (Yonida, K, 2009) , Breast and ovarian cancer (Mulaomerovic, A, 2007).

Diabetic nephropathy (DN) is a specific kidney damage in diabetes mellitus (DM), accompanied by the formation of nodular glomerulosclerosis. DN can lead to the development of end-stage renal failure, requiring renal replacement therapy (Dedov, II, 2017). According to the literature, the risk of developing chronic renal failure (CRF) in patients with diabetes is 25 times higher compared to population values (Donnelly, R.2000). According to the Federal Register of Adult Patients with Diabetes Mellitus, in 2016, the detection rate of chronic kidney disease (CKD) in the Russian Federation was: with type 1 diabetes - 23%, with type 2 diabetes - 6.9%, the frequency of registration new cases of CKD increased 2 times in type 1 diabetes and 3.7 times in type 2 diabetes (Shamkhalova, 2018). The presence of late complications of diabetes, which includes DN, leads to early disability and mortality in patients with diabetes. The frequency of occurrence of DN in type 1 diabetes depends on the duration of the disease, the compensation of metabolic disorders (glycemia and lipid spectrum) since the onset of diabetes and throughout its duration, as well as the age at which the disease debuted. So, with a disease duration of less than 5 years, DN is detected in 6–18% of patients, with a disease duration of 20–30 years - in 35–40% of patients (Hovind, P,2004). The frequency of development of DN with the onset of diabetes at puberty is 45%, with the onset after 20 years - 30% (Hovind, P,2004).

DN at the preclinical stage is characterized by functional and structural changes in the kidneys (the stage of hyperfiltration and the stage of initial structural changes in kidney tissue - thickening of the basement membrane of capillaries, expansion of the mesangial matrix), which can appear in the first 5 years from the onset of the disease and are usually reversible and difficult for diagnostics. DN is mainly detected at the clinical stage, when protein appears in the urine. Late diagnosis and the development of persistent proteinuria lead to rapid progression of DN to end-stage renal failure. The use of renal replacement therapy (hemodialysis, kidney transplantation) for the treatment of patients with late stage DN (CRF) is of significant socio-economic importance. In developed countries, patients with diabetes make up 20-50% of the total number of patients requiring renal replacement therapy [aubenberger, J, K. 2005]. The identification and introduction into clinical practice of early non-invasive markers of the preclinical stage of DN, as well as the timely appointment of nephroprotective therapy, is an urgent and important task to improve the quality of life of patients with diabetes, reduce disability and mortality, and reduce the cost of treating end-stage renal failure. The most promising for the timely diagnosis of DN is the determination of the level of cystatin C in the blood serum and the glomerular filtration rate (GFR) using this indicator.

GFR - an indicator of the filtration capacity of the kidneys, is used to establish the stage of CKD. Accurate knowledge of GFR is essential for assessing kidney function and predicting kidney function, including during planning and during pregnancy.

Several methods for calculating the GFR are currently known. The gold standard for the determination of GFR is the exogenous clearance method for assessing renal function. These

techniques are difficult to use and have a high cost, and therefore are not used in wide clinical practice (Abboud, O, 2012 , Smirnov A.V. 2012). Rehberg-Tareev test is a method for determining GFR based on an assessment of the clearance of endogenous creatinine. To carry out a sample, it is required to calculate the volume of daily urine, the concentration of creatinine in the daily urine and in the blood serum taken after the test (Proba, R-T,2010). The disadvantages of this method include the need for daily collection of urine, which is an inconvenience for the patient, due to errors in the collection or calculation of the volume. In addition, in patients with stage 3b–5 CKD, GFR may be "overestimated" due to increased tubular creatinine secretion (Smirnov, A.V. 2012). Nevertheless, the use of this method is preferable in patients with non-standard body weight and in the situation of acute renal injury assessment (Abboud, O,2012, Arutyunov, G.P.2009). The MDRD formula was proposed in 1999 by a group of experts based on data from the MDRD (Modification of Diet in Renal Disease) study, and in 2006 it was changed to take into account the use of standardized methods for calculating creatinine (Arutyunov, G.P, 2009, Tangri, N, ,2011). The advantage of this formula is that there is no need to collect daily urine, which is convenient in outpatient practice and in the case of screening studies. However, the MDRD formula is considered insufficiently accurate for determining GFR at values above 60 ml/min/1.73m^2, as well as among representatives of the Mongoloid race and some other ethnic groups (Smirnov, A.V,2012, Fabbian, F, ,2013,Delanaye, P,2014).

In 2009–2011 The same group of researchers developed a more accurate method for calculating GFR, which can be used at any stage of CKD and in representatives of all races - the CKD-EPI equation. The formula is based on a database of 8254 patients. When calculating GFR using this formula, as well as in the MDRD formula, race, gender, age of the patient and serum creatinine concentration are taken into account, no daily urine collection is required. It is the CKD-EPI formula that is recommended by KDIGO experts as a screening method for detecting kidney damage.

However, the use of calculation methods for assessing GFR is inappropriate in the case of non-standard body sizes (patients with amputation of limbs, bodybuilders), severe underweight or obesity (body mass index (BMI) <15 and> 40 kg/m^2), pregnancy, diseases of skeletal musculature (muscular dystrophy), a vegetarian diet, as well as in the case of a rapid decrease in renal function, when deciding whether to start renal replacement therapy, in patients with a renal transplant and, if necessary, prescribe toxic drugs excreted by the kidneys (for example, chemotherapy) (Smirnov, A.V, 2012) .

Cystatin C appears to be a promising marker of impaired renal function. Its level in the blood, to a lesser extent than the level of creatinine, depends on muscle mass, the amount of protein food in the diet, as well as gender, age and race (Abboud, O, 2012, Delanaye, P.2007, Stevens, L.A.2009, Peralta, C.A, 2009). The CKD-EPI research group developed formulas for determining GFR by cystatin C (CKD-EPI$_{cys}$) and by levels of both cystatin C and creatinine (CKD-EPIcr-$_{cys}$) in the blood based on data from 5352 people. The formulas were validated against GFR in 1119 study participants. When using the combined formula CKD-EPIcr-$_{cys}$, the risk of error in calculating GFR is more than 30% significantly lower than when using formulas based only on creatinine or cystatin C levels (8.5 versus 12.8 and 14.1, respectively , p <0.001) [Delanaye, P, 2007]. As a consequence, in 2012, the KDIGO clinical guidelines proposed to use the calculated GFR formulas CKD-EPI$_{cr-cys}$ or CKD-EPI$_{cys}$in patients with GFR 45-59 ml/min

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/1.73 m^2 and the absence of other markers of kidney damage in order to clarify if they have CKD, as well as in diagnostically unclear situations (Abboud, O, 2012).

Despite the potential of using cystatin C for calculating GFR, it is necessary to take into account a number of factors that can affect the level of cystatin C: thyroid status, glucocorticosteroid therapy, the presence of obesity, and measurement errors in acute kidney injury. Manetti et al. studied 181 patients with thyroid diseases and found that the level of cystatin C was statistically significantly higher in patients with clinical hyperthyroidism and lower in patients with subclinical and clinical hypothyroidism (Manetti, L, 2014). Upon reaching the euthyroid state during therapy, the level of cystatin C returned to the reference values (Manetti, L.2014). Glucocorticosteroid therapy also has an effect on cystatin C levels (Abboud, O, 2012, Poge, U, 2004, Bjarnadottir, M,1995). In particular, the values of cystatin C in the blood increased by 15% after the initiation of dexamethasone therapy (Poge, U, 2004) due to the increased expression of the cystatin C gene during treatment (Bjarnadottir, M, 1995). In addition, methods for determining GFR using cystatin C are more expensive than creatinine, and there is currently no standardization of cystatin C determination in various laboratories (Fabbian, F, 2013, Delanaye, P,2014).

Stevens et al. the presence of type 2 diabetes was associated with a higher level of cystatin C and a decrease in the level of creatinine in the blood (+8.5 and –3.9%, respectively, $p < 0.001$). In this study, cystatin C levels, to a greater extent than creatinine levels, were associated with excess weight (5.2 and 2.7%, $p < 0.001$) and BMI of patients (5.2 and 2.5%, $p < 0.001$) .Based on these findings, Stevens et al. suggested that there is a relationship between the level of cystatin C and the mass of adipose tissue (Stevens, L.A, 2009). However, Baxmann et al. the relationship between the level of cystatin C and body weight was not found, as well as between the level of cystatin C and muscle mass [Baxmann, A.C, 2008]. Given the increased incidence of obese patients with type 2 diabetes, including among women of reproductive age (Holden, SH, 2013, Peng, TY,2017), the use of cystatin C to assess GFR in this population requires additional study. It is also noteworthy that an increased level of cystatin C is a convincing marker of adverse cardiovascular events in patients with CKD. When analyzing data from the MESA study of 5759 participants, Peralta et al. found a significantly greater risk of death in the group of patients with CKD diagnosed on the basis of an increased level of cystatin C (3.23 (95% CI 1.84-5.67)) or both cystatin C and creatinine (1.93 (95% CI 1.27–2.92)) than in CKD based on elevated creatinine levels alone (0.80 (95% CI 0.50–1.26)) (Peralta, CA,.2011).

In the work of Stevens et al., Carried out on a population of patients with CKD, an increased level of cystatin C was associated with arterial hypertension (Stevens, LA, 2009). However, a number of population studies have shown that the level of cystatin C can serve as a biomarker of an increased risk of cardiovascular events, regardless of the presence of CKD (Blankenberg, S, 2010, Barr, EL, 2017). The aim of the study was to assess the possibility of determining the levels of cystatin C and GFR using the CKD-EPI_{cys} and CKD-EPIcr-$_{cys}$ formulas for early diagnosis of DN in women with type 1 diabetes at the stage of pregravid preparation and in the first trimester of pregnancy.

MATERIALS AND METHODS

The study involved 47 women with type 1 diabetes, including 25 pregnant women

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(gestational age from 7 to 12 weeks) and 22 planning pregnancy. Inclusion criteria were: duration of type 1 diabetes for more than a year, pregnancy planning, or the presence of a confirmed uterine pregnancy. Exclusion criteria were: inflammatory kidney disease, untreated hypothyroidism and hyperthyroidism, obesity, glucocorticosteroids, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists. All patients underwent general clinical examination and correction of carbohydrate metabolism. The functional state of the kidneys was assessed in each patient: the levels of creatinine and cystatin C in blood serum, protein in daily urine were determined, and the mass index was calculated. The serum creatinine concentration was determined on a biochemical analyzer UniCel D×C 600 Synchron Clinical System from Beckman Coulter using a diagnostic kit from the same company. The serum concentration of cystatin C was determined on a UniCel D×C 600 Synchron Clinical System (Beckman Coulter) biochemical analyzer using a diagnostic kit from Audit Diagnostics. GFR was calculated using the Reberg-Tareev test and formulas MDRD, CKD-EPI$_{cr}$, CKD-EPIcys, CKD-EPIcr-$_{cys}$.

The results were statistically processed using standard statistical analysis packages. Methods of descriptive statistics included an assessment of the arithmetic mean (M), the error of the mean (m) for features with a continuous distribution, and an assessment of the frequency of occurrence of features with discrete values. Fisher's exact test and Spearman's correlation coefficient were used to calculate intergroup differences. For nonparametric analysis, the general Kruskal-Wallis test was used and for pairwise comparison, the Mann - Whitney test. The critical value of the significance level (p) for testing null hypotheses was taken as $p < 0.05$.

Table 1. Show Clinical characteristics of the examined patients

Indicators	Planning pregnancy (n = 22)	Pregnant (n = 25)	P
Age. years	29.86(20–40)	32.40(22–40)	0.066
Experience. years	11.57(2–24)	11.52(1–27)	0.982
Body mass index. kg / m2	22.98(19.33–28.73)	23.03(17.53–29.74)	0.954
Glycated hemoglobin.%	8.36(5.9–12.6)	6.88(5.5–8.6)	<0.001
Pregnancy period. weeksn	–	9.5(5–14)	–
Blood creatinine. mmol / l	0.077(0.060–0.096)	0.065(0.43–0.81)	<0.001
Urine creatinine. μmol / l	11.28(8.40–13.45)	10.89(7.43–16.7)	0.501
Cystatin C. mg / l	1.00(0.73–1.56)	0.98(0.33–2.22)	0.824
Daily loss of protein. g / day	0.19(0.01–0.44)	0.20(0.03–0.90)	0.900
GFR (Reberg test). ml / min	104.4(83.0–137.0)	119.0(86.0–185.0)	0.017
GFR (EPI$_{cr}$). ml / min	90.1(66.0–135.0)	102.1(75.0–124.0)	0.005
GFR (EPI$_{cys}$). ml / min	86.3(45.0–123.0)	92.2(58.0–182.0)	0.366
GFR (EPI$_{cr-cys}$). ml / mi	84.68(59.0–156.0)	94.3(65.0–156.0)	0.046

RESULTS

We examined 47 women with type 1 diabetes. Planning pregnancy and pregnant women were comparable in age. duration of diabetes. BMI. The age of the patients ranged from 19 to 42 years: 32.4±4.1 years in the group of pregnant women and 29.9±5.1 years in the group planning

pregnancy. The duration of the disease varied from one year to 27 years and in the group of pregnant women was 11.5±8.3 years. and in the group planning pregnancy - 11.6±6.6 years. In the group planning pregnancy. the average BMI was 23.0±3.1 kg/m^2. in pregnant women - 23.0 ± 2.7 kg / m2 (Table 1).

Among the surveyed. 35 women received multiple insulin injections (MII). 12 - continuous subcutaneous insulin infusion (CPII). The average value of glycated hemoglobin in pregnant women in the first trimester was 6.9±0.9%. in those planning pregnancy - 8.4±1.7% and statistically significantly differed between groups (p = 0.001).

The groups of pregnant women and those planning a pregnancy with type 1 diabetes were statistically significantly different in blood creatinine levels (p = 0.001). as well as in the level of GFR calculated on the basis of Reberg's test (p = 0.017). EPI_{cr} (p = 0.005) and EPIcr-$_{cys}$ (p = 0.046). At the same time. there were no significant differences in urine creatinine. cystatin C. EPI_{cr} GFR and daily protein loss.

When examining a group of planning pregnancy. the GFR calculated from the Reberg test was 104 ml/min. but when calculating the GFR using cystatin C. it was significantly lower and amounted to 86.3 ml/min according to EPI_{cys} and 84.68 ml/min according to EPIcr-$_{cys}$ Similarly. in the group of pregnant women. according to the Rehberg test. the GFR was 119 ml/min. while when using the EPI_{cys} and EPIcr-$_{cys}$ formulas. the GFR decreased to 92.3 and 94.3 ml/min. respectively. In the group of pregnant women. correlations were found between the stages of GFR according to EPI_{cys} and EPI_{cr} (correlation coefficient - 0.455. p = 0.022) using Spearman's correlation coefficient. Correlation between GFR in Reberg's test and GFR calculated using the EPI_{cys} formula (correlation coefficient - 0.083. p = 0.585). as well as GFR in Reberg's test and serum cystatin C level (correlation coefficient - 0.022. p = 0.887) in both groups was not found. The majority of pregnant women. when determining GFR using the EPIcr formula. belonged to stage C1 (87.5%) and only 12.5% to stage C2. which statistically significantly differed from the group of patients planning a pregnancy. in which the percentage of patients with stages of decrease in GFR C1 and C2 proved to be comparable (p = 0.002) (Fig. 1). When GFR was staged according to the EPI_{cys} formula. the majority of pregnant women also had stage C1. while most of those planning a pregnancy were at stage C2. However. no statistical significance was obtained in this case. It is noteworthy that the C3a stage in both groups was established exclusively when calculating GFR using EPI_{cys} (Fig. 2). When staging GFR based on the results of the Rehberg test. the majority of women from both groups were classified as stage C1. and the percentage of women with stages C1 and C2 in the groups planning pregnancy and pregnant women did not differ significantly (Fig. 3).

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Chronic kidney disease stage

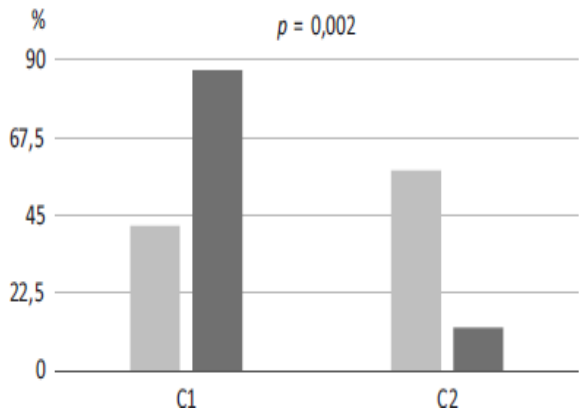

Fig. 1. The frequency of detection of chronic kidney disease when calculating the glomerular filtration rate using the CKD-EPIcr formula in the group of planning pregnancy and pregnant women

Planningapregnancy
Pregnant

Chronic kidney disease stage

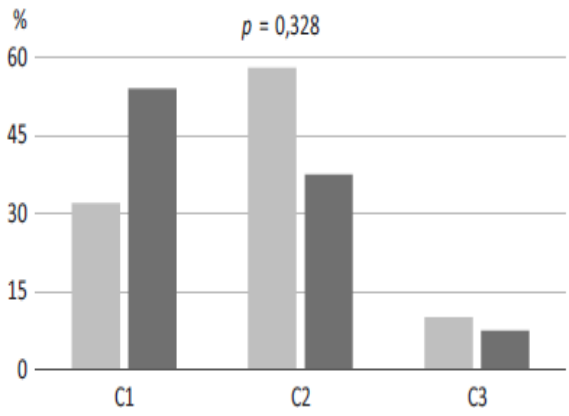

Fig. 2 . The frequency of detection of chronic kidney disease when calculating the glomerular filtration rate using the CKD-EPI_{cys} formula in the group of planning pregnancy and pregnant women

Planningapregnancy
Pregnant

A nonparametric analysis using the Kruskal - Wallis test in the groups planning pregnancy and pregnant women did not reveal differences in the level of glycated hemoglobin, the history of diabetes mellitus, BMI, the level of blood creatinine and daily protein loss depending on the stage of GFR according to EPIcys. In a nonparametric analysis using the Mann-Whitney test in the group of planning pregnancy and pregnant women, no differences were also found in the level of glycated hemoglobin, the experience of diabetes mellitus, BMI, gestational age, the level of blood creatinine, cystatin C and daily protein loss depending on the GFR stage in the sample. Reberga. However, depending on the stage of GFR according to EPI_{cr}, significant differences were obtained in the level of cystatin C ($p = 0.035$) in the group of pregnant women. In the group planning pregnancy, such a difference was not found.

DISCUSSION

Despite the encouraging results from the use of cystatin C for calculating GFR, there are a number of factors that need to be taken into account that can affect the level of cystatin C and, as a result, the interpretation of the assessment of renal function. There is a risk of laboratory error when determining the level of cystatin C in the blood. In 2011, the Institute for Reference Materials and Measurements (IRMM) issued a certified reference material ERMDA471 / IFCC, which made it possible to calibrate the results for the determination of cystatin C in blood. However, according to the researchers, the immunological methods for assessing cystatin C currently used in clinical practice are not accurate enough (Abboud O, 2012, Delanaye, P,2007). A possible reason for the error in assessing the level of cystatin C may be the fact that blood samples frozen for 5 years were used to develop reference materials (Delanaye, P, 2007). Another reason for the increase in the level of cystatin C in the blood may be the inflammatory process

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(Stevens, LA2009, Liu, X, 2013). Stevens et al. showed that a higher level of cystatin C is associated with an increase in the level of C-reactive protein and leukocytes in the blood (Stevens, LA, 2009). There is also evidence that smoking may affect cystatin C levels (Liu,X,2013).

The prospect of using cystatin C as a marker of decreased renal function in diabetes mellitus is interesting. According to Oberbauer et al., In patients with type 1 diabetes, microalbuminuria, and normal GFR measured by iothalamate clearance,

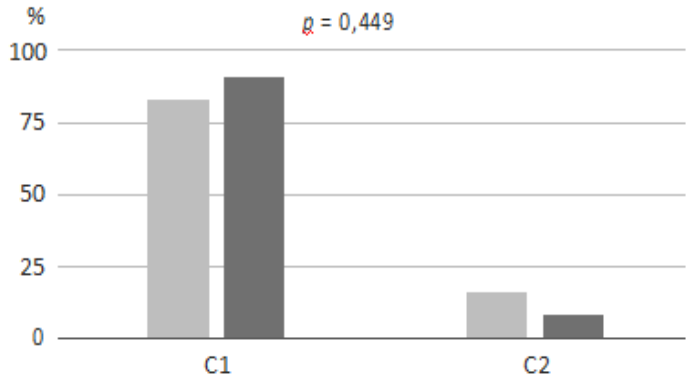

Fig. 3. The frequency of detection of chronic kidney disease when calculating the glomerular filtration rate according to the Reberg test in the group of planning pregnancy and pregnant women thus

Planningapregnancy
Pregnant

the level of cystatin C was significantly higher compared with the control group (1.27 ± 0.18 and 0.52 ± 0.15 mg / l, p <0.05) due to a decrease in the size of the filtration gaps of the renal glomeruli (53.3 ± 0.7 and 54.8 ± 0.8 Å, p <0.05) [Oberbauer, R, 2001]. Thus, it seems appropriate to study the level of cystatin C as a marker of DN progression in patients with type 1 diabetes.

T. Le Bricon, E. Thervet showed that when calculating GFR based on creatinine level, the result can be overestimated by 30% [Le, Bricon 2000]. L. Pucci compared the accuracy of calculating GFR using the Cockcroft-Gault and MDRD formulas in 128 patients with type 1 diabetes. It turned out that GFR values calculated using cystatin are more sensitive for early detection of renal dysfunction, especially in the GFR range from 90 to 75 ml/min (Pucci, L, 2007). In addition, in a study of 85 patients with type 1 diabetes, the dynamics of changes in GFR (gold standard) was measured for 10.1 years. During this time, an average of 5.6 measurements were made for each patient. The baseline mean GFR in this cohort corresponded to the reference range (106.1±2.6 ml/min/1.73 m^2). The rate of GFR decline (ΔGFR) was calculated using linear regression. A decrease in renal function was observed in 19 patients, whose ΔGFR values were> 3.3ml/ min/1.73m^2 per year. In such patients, the average values of ΔGFR were: 1) according to the gold standard - 6.5 ml/min/1.73 m^2; 2) by the level of cystatin C - 6.1 ml/min/1.73 m^2; 3) by the level of serum creatinine - 4.2 ml/min/1.73 m2; 4) according to the Cockcroft - Gault formula - 3.6 ml/min/1.73 m^2 and 5) according to the MDRD formula - 3.4 ml/min/1.73 m^2. The authors

believe that in the population of individuals with type 1 diabetes with initially normal GFR values, cystatin C is a more accurate indicator of the degree of decline in renal functions than methods based on creatinine levels (Premaratne, E, 2008). In a study by Perkins et al. included two groups of patients with type 1 diabetes - 286 patients with normoalbuminuria and 248 patients with microalbuminuria with normal GFR values. For 4–10 years, the dynamics of GFR, calculated using the formula eGFRcr-$_{cys}$. It was found that a decrease in GFR of more than 3.3% per year was observed in 10% in the group with normoalbuminuria and 35% in the group with microalbuminuria (Perkins, BA,2007). In another study, the authors evaluated GFR in terms of creatinine, cystatin C, and urinary albumin. The study involved patients with type 1 diabetes, who were divided into three groups: with normoalbuminuria (n = 63), microalbuminuria (n = 30), macroalbuminuria (n = 32). The results obtained demonstrated that GFR, calculated by the level of cystatin C, correlated with the degree of albuminuria, which indicates the reliability of the indicator as an earlier marker of changes in renal function in patients with diabetes (Domingueti, CP, 2016).

According to a number of researchers (Le, Bricon 2000, Pucci, L,2007, Premaratne, E, 2009), cystatin C is a more accurate marker of decreased renal function in DN. In our study, the GFR calculated using cystatin C was significantly lower than in the Reberg test, which made it possible to diagnose early changes in GFR in DN and promptly start nephroprotective treatment at the stage of pregravid preparation, in case of pregnancy, promptly start prophylaxis of gestosis. With pronounced kidney damage, starting with stage 3 CKD, it is possible to “overestimate” the GFR index according to Rehberg's test due to increased tubular secretion. Determining the level of cystatin C and GFR using this indicator will make it possible to more accurately establish the stage of CKD, which is especially important if the patient has absolute contraindications for prolonging pregnancy (Qasim and Al-Mayali, 2019).

CONCLUSION

Thus, the results of the study showed that the determination of the serum level of cystatin C and the glomerular filtration rate using this indicator increases the reliability of the diagnosis of kidney damage in patients with type 1 diabetes with a normal level of creatinine in the blood and the absence of a decrease in GFR calculated using creatinine. The data obtained substantiate the feasibility of determining this marker in routine clinical practice in patients with type 1 diabetes.

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