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GALECTIN-3 IN RECIPIENTS WITH KIDNEY GRAFT DYSFUNCTION: ANALYSIS OF PREDICTIVE SIGNIFICANCE

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One of the most pressing issues in contemporary transplantology is the ongoing search for less invasive methods that would identify potential complications that recipients of solid organ transplants may encounter. Profibrogenic factor galectin-3 (Gal-3) is a potential marker of such complications. It is presumed that it may be involved in regulatory processes in both physiological and pathological conditions; Gal-3 is of particular importance in diseases associated with chronic inflammation and fibrosis. **Objective:** to assess the predictive significance of Gal-3, determined in the recipients' serum, in the pathology of a transplanted kidney. **Materials and methods.** The study included 138 kidney recipients aged from 5 to 68 years and a group of healthy individuals (n = 11). Recipients' serum Gal-3 levels were measured by immunoenzymatic method. **Results.** Among the kidney recipients, 91 patients had kidney graft dysfunction according to laboratory and clinical data, which served as an indication to perform a graft biopsy with morphologic examination of the samples. In kidney recipients, Gal-3 levels were significantly different and higher than in healthy individuals, p = 0.017; it did not correlate with most blood test parameters, but there was an inverse correlation with graft glomerular filtration rate (GFR) (r = –0.174; p = 0.043). Recipients' Gal-3 levels were independent of their tacrolimus blood levels. Kidney recipients with graft dysfunction had considerably higher Gal-3 levels (p = 0.0003) compared to those without. Comparative analysis significantly showed higher Gal-3 concentrations in recipients with acute cellular rejection (ACR, p = 0.005), antibody-mediated rejection (AMR, p = 0.016) and calcineurin inhibitor (CNI) nephrotoxicity (p = 0.006) compared to recipients without dysfunction. Recipients with signs of CNI nephrotoxicity tended to have higher Gal-3 levels when compared to recipients with graft dysfunction of other etiology (p = 0.08). Kidney recipients with Gal-3 levels above the calculated threshold value of 7.63 ng/mL had a 2.89-fold higher risk of developing chronic graft dysfunction and/or requiring hemodialysis compared with the rest of the kidney recipients (RR = 2.89 ± 0.46 [95% CI 1.17–7.11]), with 76.2% sensitivity and 56.1% specificity of the test. **Conclusion.** The threshold serum Gal-3 level in kidney recipients can be considered a predictor of an unfavorable graft outcome (chronic graft dysfunction and/or a need for renal replacement therapy).

Keywords: galectin-3, kidney transplantation, graft disease, non-invasive diagnosis.

INTRODUCTION

Chronic kidney disease (CKD) is an irreversible and progressive disease that leads to end-stage renal disease and cardiovascular complications, which cause significant mortality in the population [1]. Patients with end-stage CKD require renal replacement therapy through hemodialysis, peritoneal dialysis or kidney transplantation. Although the mortality rate in dialysis patients has decreased in recent decades [2, 3], it still remains higher compared to the general population [4]. Kidney transplantation (KT) is the most desired treatment for end-stage CKD because it achieves a higher survival rate and quality of life, and reduces cardiovascular complications. In addition, KT has a lower cost than dialysis procedures [5–7].

Puncture biopsy of the graft is currently used to diagnose and confirm post-transplant complications in kidney recipients. Clinical signs of kidney graft dysfunction that have already developed due to immune damage or another injury are indications for an unscheduled biopsy. In addition, there is a risk of taking a non-diagnostic section of the transplanted kidney tissue for examination. It is evident that with early minimally invasive diagnosis, immunosuppressive therapy can be corrected early, preventing the development of kidney graft dysfunction or reducing its severity.

In this regard, in recent years, research has been actively conducted in the search for personalized methods of minimally invasive diagnostics of post-transplant complications based on analysis of the levels of molecular and genetic biomarkers, as well as their combinations

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[8]. The minimally invasive technology for biomarker quantification is based on measuring their concentration in blood and other biological media. Such biomarkers include profibrogenic factor galectin-3 (Gal-3), which has multiple effects in physiological and pathological processes. Gal-3 is a beta-galactoside-binding protein with a unique structure of polypeptide domains that allows it to interact with proteins in carbohydrate-dependent and -independent ways.

Gal-3 stimulates the chemotaxis of macrophages and monocytes, adhesion of neutrophils and activation of proinflammatory factors. Gal-3 has been shown to play a role in chronic inflammatory diseases and tissue fibrosis [9]. There is evidence of a connection between changes in serum Gal-3 levels in solid organ recipients: heart and lungs [10, 11], liver [12], kidneys [13], with the development of post-transplant complications. Assessing Gal-3 levels in recipients may be useful for improving the methods for early diagnosis of transplant pathology.

The aim of the present work is to evaluate the predictive significance of serum Gal-3 levels in recipients, in the pathology of a transplanted kidney.

MATERIALS AND METHODS

The study included 138 adult kidney recipients who underwent related kidney allotransplantation (RKAT) or cadaveric kidney allotransplantation (CKAT) from 1999 to 2022 at Shumakov National Medical Research Center of Transplantology and Artificial Organs.

The selected recipients included 91 with signs of graft dysfunction that required unscheduled puncture biopsy and 47 without signs of graft dysfunction. The dysfunction criteria were considered to be elevated creatinine and urea levels, as well as proteinuria. The comparison group consisted of 11 healthy individuals selected randomly and not significantly different in terms of age and gender from the kidney recipients. All recipients underwent routine examinations following KT, in accordance with the Shumakov Center's patient management protocol and the National Clinical Guidelines of the Russian Transplant Society. These examinations included a clinical evaluation, full blood count, biochemical blood tests and urine tests, measurement of blood tacrolimus levels, graft biopsy, and measurement of glomerular filtration rate (GFR).

Gal-3 levels were determined in venous blood serum. For this purpose, blood samples collected in disposable tubes were centrifuged, after which the serum was frozen and stored at -20 °C. Gal-3 concentration was measured by enzyme-linked immunosorbent assay using a specific reagent kit (Human Gal-3 ELISA Kit, RayBio®, USA) according to instructions. Blood samples for Gal-3 level analysis were collected on the day of biopsy and other routine laboratory tests (full blood count, biochemical blood tests, and general urinalysis).

All kidney recipients received standard triple-combination immunosuppressive therapy, including a combination of calcineurin inhibitors (tacrolimus, less frequently cyclosporine) in combination with mycophenolate and corticosteroids, and additional drug therapy as indicated.

The indication for puncture biopsy was renal graft dysfunction presenting as increased blood creatinine levels, either alone or in combination with proteinuria, as well as a marked decrease in GFR. The pathology of the transplanted kidney was verified on the basis of the morphological studies of the biopsy material according to the Banff classification. Sections of the obtained samples were stained with hematoxylin, eosin, Masson's trichrome and Periodic acid-Schiff (PAS).

The following pathology variants were identified: acute tubular necrosis in the early post-transplant period (ATN), acute cellular rejection (ACR), antibody mediated rejection (AMR), nephrosclerosis with signs of calcineurin inhibitor (CNI) nephrotoxicity, not associated with immune response (CNI nephrosclerosis), and recurrent glomerulonephritis of the transplant (chronic glomerulonephritis). Given the morphological study results, the recipients' immunosuppressive therapy was adjusted.

The development of chronic dysfunction against the backdrop of the ineffectiveness of the current therapy, or the need for renal replacement therapy (hemodialysis or peritoneal dialysis) in conjunction with minimizing immunosuppressive therapy while waiting for re-transplantation, were deemed criteria for an unfavorable outcome of graft condition.

The graft GFR was calculated using the CKD-EPI formula, which takes into account race, sex, age, and serum creatinine level.

Nonparametric statistics methods – Mann–Whitney U test and Spearman correlation – were used for comparative analysis of independent variables. Group differences were considered reliable at $p < 0.05$. The predictive significance of Gal-3 level was evaluated using ROC analysis. The optimal threshold level for predicting high risk of adverse KT outcome was determined using the Youden's index. The main diagnostic characteristics of the test were evaluated: relative risk (RR), 95% confidence interval (CI) limits, sensitivity (Se), and specificity (Sp). Software package Statistica v.13.0, StatSoftInc (USA) was used for statistical processing of the obtained data.

RESULTS

The study included 138 kidney recipients aged 5 to 68 years, among whom the number of men 68 (49.3%) and women 70 (50.7%) did not differ significantly.

The major proportion of patients (74.7%) underwent CKAT and the remaining 25.3% received a living RKAT. The follow-up period of the recipients ranged from 2 to 4,748 days (median, 325 days); 75% of the patients were examined in the long term (more than 1 month from the

date of transplantation). The main characteristics of the recipient group are presented in Table 1.

Serum Gal-3 levels of the subjects included in the study varied within a wide range of 5.8 [1.9; 17.8] ng/mL, did not differ significantly between men and women (p = 0.77), and did not correlate with age (r = –0.15; p = 0.14).

Gal-3 levels in kidney recipients was significantly different and higher than in healthy individuals, p = 0.017. Comparative analysis of Gal-3 concentration in those who received related kidney and a kidney from a postmortem donor revealed no significant differences (p = 0.083).

There was no significant correlation between Gal-3 levels and post-transplant period (days) (r = 0.125; p = 0.24); There were no significant differences in Gal-3 level in kidney recipients in the early (<30 days) and late (>30 days) post-transplant period (p = 0.57).

Table 1

Basic characteristics of kidney recipients and healthy subjects included in the study

Parameter		Kidney recipients	Healthy subjects
Number (n)		138	11
Gender (n (%)):	Male	68 (49.3%)	6 (55%)
	Female	70 (50.7%)	5 (45%)
Age (years):	Range Median [Interquartile range]	5 to 68 37 [26; 48]	10 to 64 44 [29; 54]
Type of transplant (n (%)):	Deceased donor (CKAT)	101 (73%)	–
	Living-related donor (RKAT)	37 (27%)	
Graft function (n (%)):	Normal function	47 (34%)	–
	Signs of graft dysfunction	91 (66%)	
Follow-up period (days):	Range Median [Interquartile range]	2 to 4748 325 [39; 1448]	–
Post-transplant period (n (%)):	Early (≤1 month)	34 (25%)	–
	Late (>1 month)	104 (75%)	
Gal-3 level (ng/mL):	Median [Interquartile range]	7.6 [1.9; 24.1]	2.75 [1.64; 3.11]

Table 2

Correlation of Galectin-3 levels with complete blood count, biochemical tests and urinalysis indicators in kidney recipients

Indicator	Spearman's rank correlation (r)	Significance level (p)
Complete blood count		
Hemoglobin (g/L)	r = –0.023	p = 0.870
White blood cells (10^9/L)	r = –0.191	p = 0.185
Platelets (10^9/L)	r = –0.164	p = 0.249
Blood chemistry test		
Total protein (g/L)	r = –0.021	p = 0.083
Creatinine (μmol/L)	**r = 0.179**	**p = 0.039**
Urea (mmol/L)	r = 0.169	p = 0.051
ALT (U/L)	r = 0.069	p = 0.476
AST (U/L)	r = –1.737	p = 0.083
Special blood test		
GFR (mL/min/1.73 m^2)	**r = –0.174**	**p = 0.043**
Tacrolimus (ng/mL)	r = –0.122	p = 0.183
Urinalysis		
Red blood cells (in the field of view)	**r = 0.176**	**p = 0.048**
White blood cells (in the field of view)	r = 0.132	p = 0.139
Proteinuria (g/L)	r = 0.002	p = 0.982

The relationship between Gal-3 concentration and the main indicators of complete blood count, biochemical tests and urinalysis was studied (Table 2).

Correlation analysis showed that Gal-3 level did not correlate with most blood test parameters, but it did correlate directly with creatinine level (r = 0.179; p = 0.039) and inversely with graft GFR (r = –0.174; p = 0.043). Recipients' tacrolimus concentrations did not affect Gal-3 levels.

Evaluation of the relationship between serum Gal-3 levels and urinalysis parameters showed a significant direct correlation with red blood cell count (r = 0.176; p = 0.048).

Out of all 138 recipients included in the study, 91 were categorized as "with graft dysfunction" and 47 were designated as "with normal function" based on laboratory and clinical data. Comparative analysis of the values of laboratory parameters in recipients with and without graft dysfunction is shown in Table 3.

Kidney recipients with graft dysfunction had significantly higher levels of creatinine and urea, GFR and proteinuria (p < 0.00001) compared to those without.

Comparative analysis of serum Gal-3 levels in these groups also showed significant differences (p = 0.0003).

A comparative analysis of Gal-3 levels in the blood of kidney recipients with and without graft dysfunction of different nature was carried out (Fig. 1).

It was found that in recipients with ACR (n = 29), AMR (n = 35) and CNI nephrosclerosis (n = 10), Gal-3 levels were significantly higher than in recipients with normal graft function (p = 0.005, p = 0.016 and p = 0.006 respectively).

There were no significant differences in Gal-3 levels in acute tubular necrosis (n = 11) and recurrent glomerulonephritis (n = 6) compared to recipients without graft dysfunction (p = 0.056 and p = 0.083, respectively).

No significant differences were found in a comparative analysis of Gal-3 levels in kidney recipients with graft dysfunction depending on the nature of the pathology. This may be due to the small patient sample size. On the other hand, receivers exhibiting signs of CNI nephrotoxicity tended to have higher Gal-3 levels than recipients experiencing graft dysfunction of other etiology (Fig. 2).

Table 3

Comparative analysis of laboratory parameters in kidney recipients with and without graft dysfunction

Indicator	Normal function	Graft dysfunction	Significance level
Creatinine (μmol/L)	85.3 [69.9; 97.83]	214.9 [151.7; 363.8]	**p < 0.00001**
Urea (mmol/L)	7.4 [5.9; 8.5]	18.52 [12.8; 26.2]	**p < 0.00001**
Proteinuria (g/L)	0.04 [0.03; 0.19]	0.14 [0.04; 0.40]	**p < 0.00001**
GFR (mL/min)	81.5 [70.23; 102.9]	26.34 [14.3; 43.7]	**p < 0.00001**
Gal-3 (ng/mL)	2.3 [0.06; 14.4]	8.75 [3.5; 28.5]	**p = 0.0003**

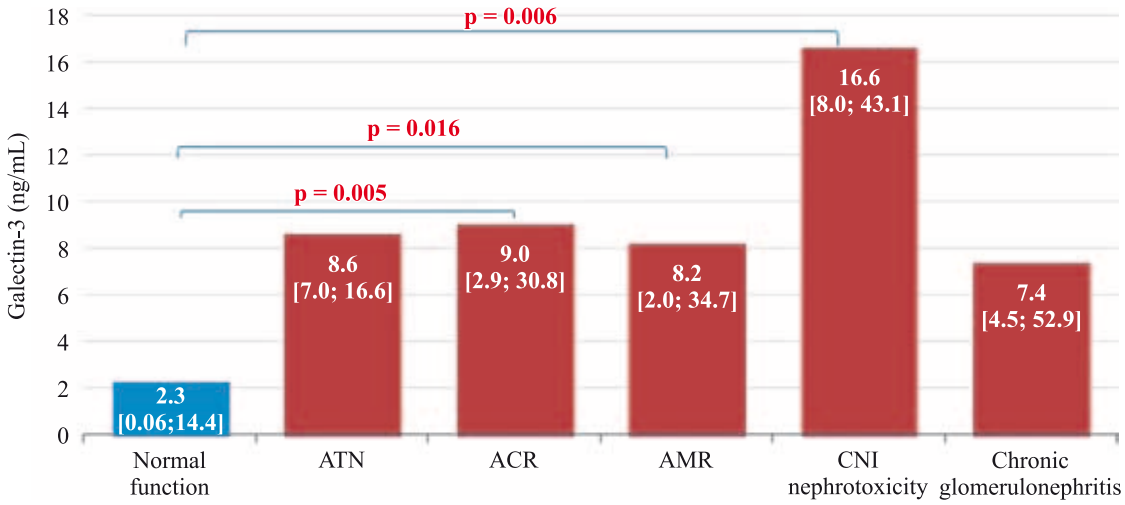

Fig. 1. Comparative analysis of Serum galectin-3 levels in kidney recipients with and without graft dysfunction of various natures. ATN, acute tubular necrosis; ACR, acute cellular rejection; AMR, antibody-mediated rejection; calcineurin inhibitor (CNI) nephrotoxicity

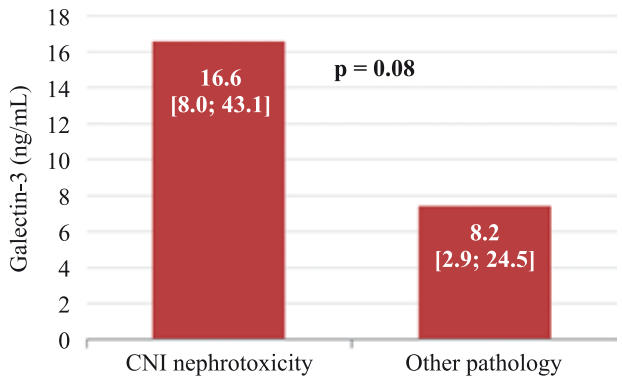

Fig. 2. Comparative analysis of galectin-3 levels in kidney recipients with signs of calcineurin inhibitor nephrotoxicity and other lesions

At the same time, in the level of classical renal function parameters (creatinine, urea, proteinuria and GFR), there was no tendency for difference in the recipients with signs of CNI nephrotoxicity compared to recipients with graft dysfunction of other etiology (Table 4).

Among kidney recipients in whom graft dysfunction was verified, 21 patients at long-term follow-up (13.6 [1.2; 48.3] months) developed an unfavorable graft outcome (chronic graft dysfunction and/or need for hemodialysis), while 57 patients had preserved graft function.

A comparative analysis of serum Gal-3 levels in kidney recipients and GFR, determined six months (5.4

Table 4

Comparative analysis of laboratory parameters of renal graft function in kidney recipients with signs of calcineurin inhibitor nephrotoxicity and other lesions

Indicator	CNI nephrotoxicity	Other pathology	Significance level
Creatinine (μmol/L)	186.6 [142; 259]	212.3 [149.1; 356.4]	p = 0.56
Urea (mmol/L)	16 [13.1; 20.7]	18.5 [12.5; 27.4]	p = 0.66
Proteinuria (g/L)	0.08 [0.04; 0.34]	0.14 [0.04; 0.40]	p = 0.53
GFR (mL/min)	31.4 [15.1; 38.7]	26.3 [14.3; 44.7]	p = 0.88

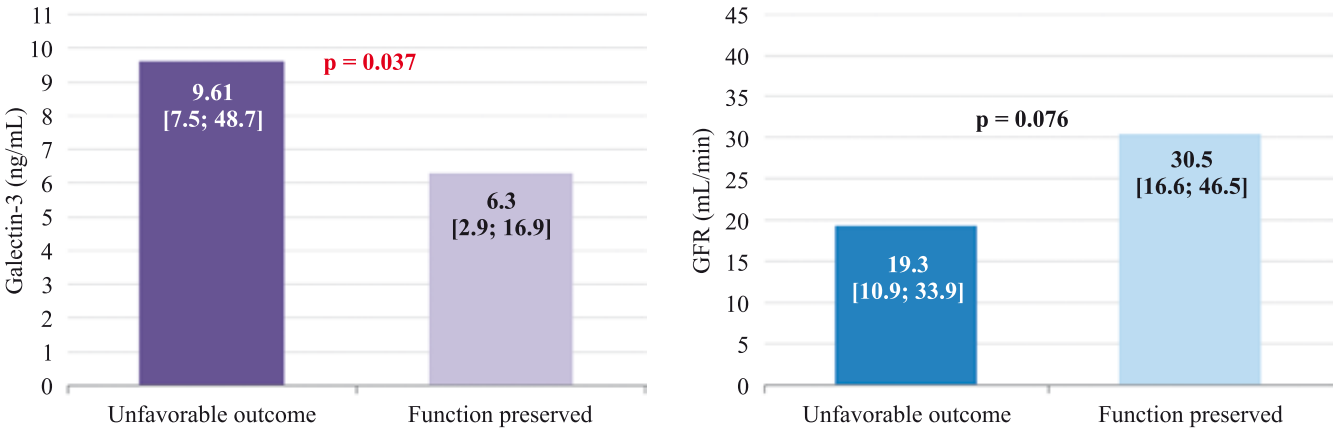

Fig. 3. Comparative analysis of baseline galectin-3 and GFR levels in kidney recipients with and without unfavorable graft outcome

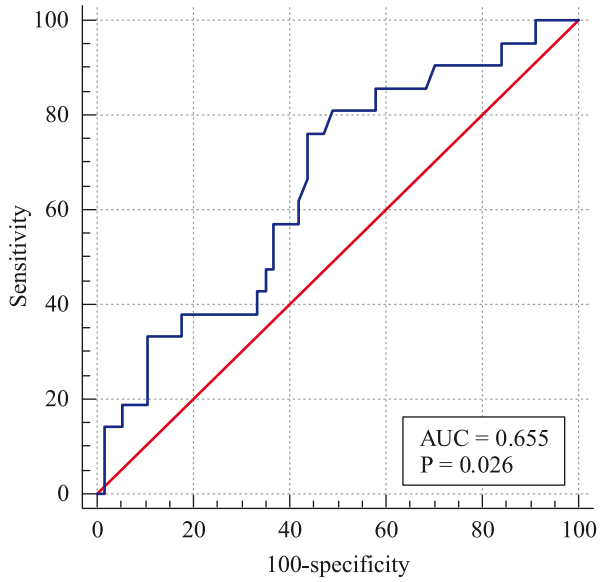

Fig. 4. ROC curve of serum galectin-3 levels in kidney recipients with unfavorable graft outcome

Table 5

Comparative analysis of kidney graft outcome and galectin-3 levels

Outcome	Recipients with Gal-3 levels >7.63 ng/mL (n = 41)	Recipients with Gal-3 levels ≤7.63 ng/mL (n = 37)	Significance (p)
Unfavorable	16 (39%)	5 (14%)	**0.021**
Favorable	25 (61%)	32 (86%)	

[1.8; 8.3] months) before the onset of an unfavorable graft outcome, was performed with the same indicators in patients with preserved graft function (Fig. 3).

It was found that the initial serum Gal-3 concentrations in kidney recipients were significantly higher in patients with chronic graft dysfunction and/or need for hemodialysis compared to recipients without it (p = 0.037). Baseline GFR scores did not differ between these recipient groups.

An assessment of the predictive significance of serum Gal-3 level in kidney recipients in relation to the development of unfavorable post-transplant outcome is presented in Fig. 4.

The area under the ROC curve was 0.655 ± 0.069 [95% CI 0.538–0.759] and was significantly (p = 0.026) different from 0.5.

The threshold serum Gal-3 level in kidney recipients, significant for predicting adverse graft outcome, was 7.63 ng/mL (Table 5).

Among 41 kidney recipients with Gal-3 level >7.63 ng/mL, 16 (39%) had an unfavorable kidney transplant outcome, which is significantly different from the group of recipients with Gal-3 ≤7.63 ng/mL, in which 5 (14%) out of 37 recipients had unfavorable outcome (p = 0.021).

Analysis of the predictive characteristics of Gal-3 level in relation to graft outcome in kidney recipients showed that in kidney recipients with Gal-3 level exceeding the threshold 7.63 ng/ml, the risk of developing

chronic graft dysfunction and/or requiring hemodialysis was 2.89 times higher than in the rest of kidney recipients with graft dysfunction (RR = 2.89 ± 0.46 [95% CI 1.17–7.11]), with a 76.2% sensitivity and 56.1% specificity.

DISCUSSION

The development in recent years of innovative approaches to the diagnosis and prediction of post-transplant complications has become possible due to active research in the field of biochemistry, immunology and genetics. Mechanisms of interaction between the recipient's body and the donor organ include a wide range of immunological responses that can lead to graft rejection [14]. After transplantation, recipients are still likely to develop ACR, AMR and chronic rejection, which lead to accelerated formation of graft fibrosis and graft dysfunction [15].

In this regard, early detection of post-transplant complications is of key importance for long-term graft functioning [16]. Carrying out a transplant puncture biopsy to verify the pathology of the transplanted kidney is not always informative due to the risk of sampling a tissue area without morphological signs of changes. In addition, laboratory data on declining renal function typically serve as an indication for a biopsy and already point to a chronic pathological process in the kidney graft [17]. The use of minimally invasive laboratory diagnostic methods in kidney recipients should improve the efficiency of detecting graft pathology at an early stage of development.

A large number of studies show that Gal-3 plays an important role in the development of various pathological processes, including inflammation, immune cell infiltration and fibrosis [18, 19]. This thesis is supported by research conducted on two animal groups by Dang et al. They found that mice with a genetic defect in Gal-3 in their kidney transplant had less tubular injury, moderate fibrosis and lower immune cell infiltration in comparison to the group of normal animals, in which characteristic changes in the transplant were determined in the form of renal tubular atrophy, as well as Gal-3 upregulation in tissues and blood plasma [13].

Another study showed that pharmacological suppression (modified citrus pectin) or genetic switching off of Gal-3 inhibited the upregulation of Gal-3 linked to fibrosis and renal dysfunction in models of experimental hyperaldosteronism [20].

In our study, it was shown that there was no correlation between Gal-3 levels and most laboratory blood test parameters, which suggests the independent diagnostic potential of Gal-3. At the same time, there was an inverse correlation between serum Gal-3 levels in the kidney recipients and transplant GFR ($r = –0.174$; $p = 0.043$).

These findings are consistent with those of Alam M.L. et al., who found that higher Gal-3 levels were associated with CKD progression and lower GFR <15 mL/min [21]. A study by Hsu B.G. et al. discovered an inverse correlation between serum Gal-3 level in CKD patients and GFR. In addition, it was suggested that Gal-3 is a potential modulator of endothelial function and can be used as a biomarker to diagnose endothelial dysfunction in patients with kidney injury [22].

CNIs occupy a special place among immunosuppressive drugs that prevent transplant rejection. The introduction of this group of drugs into daily clinical practice has improved survival rates and quality of life of solid organ recipients. However, the need for lifelong CNIs leads to a number of side effects, among which the nephrotoxic effect with the development of CNI nephrosclerosis is of particular importance in kidney transplant recipients [23]. In this study, no significant differences were found in a comparative analysis of Gal-3 levels in kidney recipients with graft dysfunction depending on the nature of the pathology. However, there was a tendency for higher Gal-3 levels in recipients with signs of CNI nephrotoxicity in comparison with recipients with graft dysfunction of other etiology ($p = 0.08$). This finding may be associated with fibrosis and functional remodeling of the graft in this cohort of kidney recipients.

In a study by Ou S.M. et al., it was shown that higher plasma Gal-3 levels in CKD were associated with interstitial fibrosis, tubular atrophy and vascular intima fibrosis. When evaluating RNA sequencing results, the authors showed an upregulation of Gal-3 in biopsy samples of fibrotic kidney [24].

To be able to predict kidney transplant survival, it is necessary to develop minimally invasive diagnostic methods using biomarkers to predict long-term transplant outcome. The present study evaluated the predictive significance of serum Gal-3 levels in recipients with kidney graft dysfunction in relation to the development of an unfavorable outcome (chronic graft dysfunction and/or need for dialysis). It was found that kidney recipients with Gal-3 levels exceeding the threshold value of 7.63 ng/mL have almost three times higher risk of developing chronic graft dysfunction and/or a need for dialysis compared to other kidney recipients, with a 76.2% sensitivity and 56.1% specificity. The insufficiently high specificity of the test is obviously down to the inclusion of only kidney recipients with existing graft dysfunction signs in the study group.

The threshold serum Gal-3 level in kidney recipients determined in this work can be considered as an additional test, specifically as a predictor of poor outcome of kidney transplant dysfunction, and be useful for early modification of immunosuppressive therapy and/or performance of unscheduled biopsy.

The study was conducted within the framework of state assignment.

The authors declare no conflict of interest.

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