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Expression of KIM-1, VEGF and bFGF in the transplanted kidney as predictive factors of kidney allograft function

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ABSTRACT

Introduction: Transplantation is now a common treatment for kidney failure. However, it is associated with numerous complications, among which is rejection. Currently, factors that can predict the function of the transplanted kidney are being sought. This study aimed to investigate whether the expression of kidney injury molecule-1 (KIM-1), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) assessed in the transplanted kidney before transplantation can be a predictive marker of the later function of the transplanted kidney and the occurrence of complications such as delayed graft function (DGF) and acute rejection (AR).

Material and methods: The study group included 44 kidney allograft recipients who underwent kidney transplantation.

Results: There were no statistically significant correlations between KIM-1, VEGF and bFGF gene expression in transplanted kidney biopsies and the occurrence of DGF and AR. The expression of the bFGF gene correlated significantly with the creatinine levels before and on the first day after transplantation. There were no statistically significant correlations between creatinine levels and expression of the KIM-1 and VEGF genes. There was also no statistically significant correlation between bFGF, KIM-1 and VEGF gene expression in the transplanted kidney and later eGFR and diuresis values. A statistically significant negative correlation was found between bFGF and serum potassium levels before transplantation and up to one month after transplantation. KIM-1 expression correlated significantly negatively with pre-transplant serum potassium levels. VEGF expression correlated significantly negatively with potassium levels 2 and 24 months after transplantation.

Conclusions: The present results suggest that the expression of KIM-1, VEGF and bFGF assessed in the transplanted kidney before transplantation is not a significant predictor of the later function of the transplanted kidney. The expression of the bFGF gene correlates with the creatinine levels before and on the first day after transplantation. The expression of KIM-1, VEGF and bFGF may correlate with potassium serum levels.

Keywords: KIM-1, VEGF, bFGF, kidney, allograft

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Introduction

Kidney transplantation is an established treatment for end-stage renal failure. However, many complications occur after transplantation that reduce the survival time of the transplanted kidney. Delayed graft function (DGF) is a common complication after kidney transplantation. It is defined as transient failure of the transplanted kidney, requiring dialysis therapy during the first 7 days after transplantation [1]. DGF is an independent risk factor for acute rejection (AR) and impaired renal function in the first year after transplantation. It also contributes to reduced graft survival [2–4]. One of the main causes of loss of the transplanted kidney is the rejection process [5]. Acute rejection of the graft usually develops during the first few weeks after the transplantation procedure.

The incidence of asymptomatic episodes of AR detected by biopsies ranges from 6 to 22% [6]. During the first year after transplantation, AR is the cause of a graft loss incidence of 11 to 16%, and in the following years 7 to 11% [6]. Factors affecting the long-term function of the transplanted kidney include immunological factors, such as episodes of AR, HLA mismatch between recipient and transplant donor, presence of lymphocytotoxic antibodies (PRA), and non-immunologic factors: older donor/recipient age, DGF.

Currently, the diagnosis of transplanted kidney injury is based on traditional parameters evaluating renal function, including creatinine, glomerular filtration rate (eGFR) and urea levels, the presence of proteinuria, and ultrasonographic evaluation [7]. In order to diagnose changes in the transplanted kidney, biopsy is increasingly used as a method of detecting and identifying key factors contributing to renal damage.

Currently, new methods are being sought to monitor normal graft function. These methods should make it possible to detect the risk of graft rejection early, optimize the immunosuppressive treatment regimen and distinguish the rejection reaction from other pathological conditions of the organ. The most common monitoring method after kidney transplantation is monitoring serum creatinine levels. This method is relatively simple and inexpensive but has low specificity and sensitivity. This is due to the fact that there are many factors that cause a decrease in glomerular filtration rate and an increase in serum creatinine concentration.

The search for markers of transplanted kidney function is of particular importance, as early recognition of kidney dysfunction may allow the implementation of appropriate therapy to prevent the process of graft rejection. This may allow a significant increase in the survival rate of the transplanted organ.

In the present study, it was decided to investigate whether the expression of molecules with known effects on kidney function in transplanted kidney biopsies could be a predictor of renal graft function.

This study aimed to investigate whether the expression of kidney injury molecule-1 (KIM-1), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) assessed in the transplanted kidney before transplantation can be a predictive marker of the later function of the transplanted kidney and the occurrence of complications such as DGF and AR.

Material and methods

Patients

The study group included 44 kidney allograft recipients (23 females and 21 males, aged 21 to 72 years, mean 49.95 ± 14.01), who underwent kidney transplantation at the Department of General and Transplant Surgery of Pomeranian Medical University in Szczecin. The clinical characteristics and biochemical parameters of the patients are shown in Tables 1 and 2. The study material consisted of peripheral blood obtained during routine examinations. During hospitalisation and in the 1st, 3rd, 6th and 12th months after renal transplantation, parameters of transplanted kidney function were determined from peripheral blood, i.e., creatinine concentration, eGFR, potassium level and diuresis.

Each subject was informed about the nature and purpose of the study and gave informed consent. The study was approved by the ethics committee at Pomeranian Medical University, Szczecin, Poland and written informed consent was obtained from all subjects.

Forty-four biopsies before transplantation were performed, followed by biopsies in the post-transplant period (n = 23, 52.27%). Diagnostic biopsies were performed in five patients (11.36%) due to clinical indications. From the study group, 17 patients (38.63%) with DGF were identified, with a diagnosis of AR in 5 patients (11.36%). DGF was defined as the need to start haemodialysis therapy within the first 7 days after transplantation. Acute rejection of the transplanted kidney was diagnosed based on classical clinical criteria: time after organ transplantation up to 3 months, soreness and/or swelling of the graft, increase in body temperature above 38°C, elevation of serum creatinine concentration by 10–25% over 1–2 days without any other detectable cause, or no expected decrease in serum creatinine concentration in patients during the first two weeks after transplantation. All patients were treated with immunosuppressive therapy according to a protocol: tacrolimus + mofetil mycophenolate + cyclosporine. In addition, some patients were taking additional medications due to comorbidities such as ischaemic heart disease, hypertension, diabetes mellitus, anaemia and calcium-phosphate disorders. The study was approved by the Ethics Committee of Pomeranian Medical University, Szczecin, Poland (KB-0012/40/14). Informed consent was obtained from all subjects involved in the study.

Expression analysis of KIM-1, VEGF and bFGF genes at the mRNA level using qPCR

Total RNA was isolated using the RNeasy Mini Kit (Qiagen Inc., USA). Then, 1 μg of RNA was reverse transcribed using the First Strand cDNA Synthesis Kit (Fermentas Inc., USA). Expression analysis of KIM-1, VEGF, bFGF and the BMG constitutive gene was performed by qPCR using the CFX96 Real-Time System (Bio-Rad, USA). Amplification on a cDNA array was performed using iQ™ SYBR® Green Supermix (Bio-Rad, USA) with specific primers for the studied genes designed using the Primer3 program. The relative quantitative mRNA expression of the tested genes was calculated using the comparative Ct method.

Table 1. The clinical characteristics of patients

Parameter	Mean ± SD
Age (years)	49.95 ± 14.01
Sex:	
Female	23
Male	21
BMI (kg/m^2)	25.15 ± 2.85
PRA	
Final	2.15 ± 5.72
Max	6.17 ± 11.11
IGF (n)	27
DGF (n)	17
AR (n)	5

AR — acute rejection; BMI — body mass index; DGF — delayed graft function; IGF —immediate graft function; PRA — panel reactive antibodies; SD — standard deviation

Serum creatinine was determined using a kinetic colourimetric assay according to the Jasffe method.

Serum potassium concentration was determined by an ion-selective method using selective membranes.

The glomerular filtration rate was calculated according to the formula:

$$eGFR = 170 \times Creatinine - 0{,}999 \times age - 0.176 \times BUN - 0.17 \times Albumin - 0.318 \times C$$

C — constant: for men — 1, for women — 0.762; BUN — blood urea nitrogen

Statistical analysis

The distribution of quantitative parameters differed significantly from the normal distribution (Shapiro–Wilk test), so they were compared between groups using the non-parametric Mann–Whitney test and presented as the median and interquartile range (IQR). Correlations between selected quantitative parameters were investigated using Spearman's rank correlation coefficient. P-values < 0.05 were considered statistically significant.

Table 2. Biochemical parameters of patients before transplantation and 1, 7 days and 1, 3, 6 12 months after transplantation

Parameter	Mean ± SD
Creatinine (mg/dL)	
Before transplantation	8.16 ± 3.28
1 day	7.59 ± 2.92
7 days	4.67 ± 3.85
1 month	1.84 ± 1.34
3 months	1.54 ± 0.56
6 months	1.48 ± 0.46
12 months	1.27 ± 0.35
eGFR (mL/min/1.73 m^2)	
Before transplantation	7.77 ± 4.08
1 day	8.00 ± 3.05
7 days	26.22 ± 22.31
1 month	48.74 ± 19.64
3 months	53.37 ± 21.51
6 months	51.26 ± 15.73
12 months	71.18 ± 25.05
Potassium plasma level (mmol/L)	
Before transplantation	4.77 ± 0.77
1 day	5.23 ± 0.93
7 days	4.48 ± 0.77
1 month	4.76 ± 0.70
3 months	4.60 ± 0.59
6 months	4.30 ± 0.46
12 months	4.17 ± 0.41
Diuresis (mL)	
1 day	811.90 ± 1101.27
7 days	2580.95 ± 1653.97
1 month	2900.00 ± 882.014
3 months	2878.94 ± 587.32
6 months	2652.7778 ± 427.943
12 months	2625.00 ± 595.683

eGFR — glomerular filtration rate; SD — standard deviation

Results

This study evaluated the correlation of KIM-1, VEGF and bFGF gene expression in transplanted kidney biopsies with the occurrence of DGF and AR, alongside creatinine levels, eGFR and diuresis.

As shown in Table 3, there were no statistically significant correlations between KIM-1, VEGF and bFGF gene expression in transplanted kidney biopsies with the occurrence of DGF and AR.

Tables 4–7 show the correlations between KIM-1, VEGF and bFGF gene expression and creatinine levels, eGFR, diuresis and potassium serum levels.

The expression of the bFGF gene correlated statistically significantly with the creatinine levels before and on the first day after transplantation. There were no

Table 3. VEGF, KIM-1 and bFGF expression in patients with and without DGF and with and without AR

	Patients with DGF	Patients without DGF	P-value	Patients with AR	Patients without AR	P-value
	Median value (IQR)	Median value (IQR)		Median value (IQR)	Median value (IQR)	
bFGF	87.28 (59.61–189.71)	89.12 (41.00–183.25)	0.70	94.20 (18.47–172.17)	87.89 (59.20–187.10)	0.58
KIM-1	1707.55 (890.03–1988.84)	1199.08 (451.22–1792.444)	0.38	1707.55 (1560.41–1804.91)	1199.08 (607.90–1947.91)	0.67
VEGF	283.59 (120.06–316.86)	216.50 (139.84–295.64)	0.69	299.77 (144.77–445.01)	223.28 (120.06–306.06)	0.57

AR — acute rejection; bFGF — basic fibroblast growth factor; DGF — delayed graft function; KIM-1 — kidney injury molecule-1; VEGF — vascular endothelial growth factor

statistically significant correlations between creatinine levels and expression of the KIM-1 and VEGF genes.

There was also no statistically significant correlation between bFGF, KIM-1 and VEGF gene expression in the transplanted kidney and later eGFR and diuresis values.

There was a statistically significant negative correlation between bFGF and potassium serum levels before transplantation and 1, 7 days and 1 month after transplantation. KIM-1 expression correlated significantly negatively with potassium serum levels before transplantation. The expression of VEGF correlated significantly negatively with potassium levels 2 and 24 months after transplantation.

Discussion

This study aimed to investigate whether the expression of KIM-1, VEGF and bFGF in the transplanted kidney could be used as a marker to predict its future function and the occurrence of complications such as DGF and AR. It was observed that bFGF gene expression correlated statistically significantly with creatinine levels before and on the first day after transplantation. However, no statistically significant correlations were found between creatinine levels and expression of KIM-1 and VEGF. There was also no statistically significant correlation between the expression of bFGF, KIM-1 and VEGF in the transplanted kidney and later values of eGFR and diuresis. Similarly, there was no statistically significant correlation between the expression of the studied markers and the occurrence of DGF and AR. A statistically significant negative correlation was found between bFGF and serum potassium levels before transplantation and up to one month after transplantation. KIM-1 expression correlated significantly negatively with pre-transplant serum potassium levels. VEGF expression correlated significantly negatively with potassium levels 2 and 24 months after transplantation.

Table 4. Spearman's correlations between bFGF, KIM-1, VEGF and serum creatinine levels

Creatinine	R	P-value
bFGF		
Before transplantation	–0.2984	0.0491
1 day	–0.3269	0.0303
7 days	–0.1419	0.3583
1 month	0.0203	0.8971
2 months	–0.1330	0.4073
6 months	–0.0691	0.6844
12 months	–0.1160	0.5271
KIM-1		
Before transplantation	–0.2644	0.0829
1 day	–0.2005	0.1919
7 days	–0.1000	0.5183
1 month	–0.0506	0.7473
2 months	–0.1602	0.3169
6 months	–0.0207	0.903
12 months	–0.1355	0.4595
VEGF		
Before transplantation	–0.1819	0.243
1 day	–0.2855	0.0635
7 days	–0.1102	0.4816
1 month	–0.1101	0.4878
2 months	–0.1707	0.2923
6 months	–0.0646	0.7083
12 months	–0.2743	0.1354

bFGF — basic fibroblast growth factor; KIM-1 — kidney injury molecule-1; VEGF — vascular endothelial growth factor

Kidney injury molecule-1 is a transmembrane glycoprotein of tubular origin containing a characteristic ectodomain (six cysteine immunoglobulin-like domains, two N-glycosylation domains and a Thr/Ser-Pro-rich

Table 5. Spearman's correlations between bFGF, KIM-1, VEGF and eGFR values

eGFR	R	P-value
bFGF		
Before transplantation	0.166	0.2814
1 day	0.2232	0.1453
7 days	0.0771	0.6189
1 month	–0.0821	0.61
2 months	0.0261	0.8782
6 months	–0.0816	0.6799
12 months	0.0938	0.6095
KIM-1		
Before transplantation	0.1753	0.255
1 day	0.145	0.3478
7 days	0.0653	0.6739
1 month	0.032	0.8427
2 months	0.0974	0.5661
6 months	–0.0175	0.9295
12 months	0.0671	0.7153
VEGF		
Before transplantation	0.0779	0.6197
1 day	0.1738	0.2649
7 days	0.0601	0.7018
1 month	0.0627	0.7009
2 months	0.1547	0.3676
6 months	0.0812	0.6872
12 months	0.2397	0.1939

bFGF — basic fibroblast growth factor; eGFR — glomerular filtration rate; KIM-1 — kidney injury molecule-1; VEGF — vascular endothelial growth factor

O-glycosylated domain) [8]. The first study on the role of KIM-1 in transplantation was published in 2002, where Han et al. demonstrated that patients with acute renal tubular necrosis have significantly increased KIM-1 expression in renal biopsy specimens [8]. KIM-1 expression was significantly correlated with serum creatinine level and negatively correlated with glomerular filtration rate. The authors suggest that KIM-1 is a more specific marker of early kidney damage than many other parameters used to assess kidney function to date, such as creatinine or eGFR [9].

Van Timmeren et al. demonstrated the presence of KIM-1 protein in renal tissue from patients with tubulointerstitial fibrosis and inflammation. Urinary KIM-1 levels correlated with the expression of this protein in renal tissue. High levels of KIM-1 were associated with low

Table 6. Spearman's correlations between bFGF, KIM-1, VEGF and diuresis

Diuresis	R	P-value
bFGF		
Before transplantation	0.3133	0.0434
1 day	0.0027	0.9865
2 days	0.0578	0.7161
3 days	0.0416	0.7936
4 days	0.0251	0.8748
5 days	–0.0596	0.7075
7 days	–0.2719	0.0816
1 month	–0.3960	0.0114
3 months	–0.1930	0.2458
6 months	–0.0782	0.6505
12 months	–0.0706	0.7009
24 months	–0.2696	0.3513
KIM-1		
Before transplantation	0.2435	0.1202
1 day	0.2244	0.1531
2 days	0.0701	0.6591
3 days	0.0261	0.8698
4 days	0.1002	0.5277
5 days	0.1675	0.2889
7 days	0.1559	0.3243
1 month	0.0314	0.8475
3 months	–0.0129	0.9387
6 months	0.1577	0.3584
12 months	0.2865	0.1119
24 months	–0.2262	0.4368
VEGF		
Before transplantation	0.0837	0.603
1 day	–0.0678	0.6737
2 days	0.064	0.691
3 days	0.0259	0.8723
4 days	0.0507	0.7528
5 days	0.0064	0.9683
7 days	–0.1915	0.2303
1 month	–0.2581	0.1126
3 months	–0.0769	0.651
6 months	–0.1808	0.2987
12 months	–0.1922	0.3004
24 months	–0.0574	0.8521

bFGF — basic fibroblast growth factor; KIM-1 — kidney injury molecule-1; VEGF — vascular endothelial growth factor

Table 7. Spearman's correlations between bFGF, KIM-1, VEGF and potassium serum level

Potassium	R	P-value
bFGF		
Before transplantation	–0.4922	0.0007
1 day	–0.1740	0.2587
7 days	–0.3664	0.0144
1 month	–0.3534	0.0201
2 months	–0.2912	0.0647
6 months	–0.0062	0.9710
12 months	0.1186	0.5179
24 months	–0.1770	0.5450
KIM-1		
Before transplantation	–0.3288	0.0293
1 day	–0.1652	0.2838
7 days	–0.1021	0.5095
1 month	0.0045	0.9773
2 months	0.0296	0.8543
6 months	–0.1289	0.4472
12 months	–0.1022	0.5778
24 months	–0.4580	0.0996
VEGF		
Before transplantation	–0.1736	0.2656
1 day	–0.2385	0.1235
7 days	0.1284	0.4118
1 month	–0.1743	0.2696
2 months	–0.3724	0.0180
6 months	–0.0371	0.8300
12 months	–0.2282	0.2169
24 months	–0.8138	0.0007

bFGF — basic fibroblast growth factor; KIM-1 — kidney injury molecule-1; VEGF — vascular endothelial growth factor

creatinine clearance, proteinuria and older donor age. The presence of KIM-1 protein in urine is highly specific for kidney damage [10]. It has been shown that KIM-1 can be a biomarker of nephrotoxic kidney injury associated with calcineurin inhibitor toxicity [11]. Studies indicate that KIM-1 protein expression in proximal tubules is significantly correlated with renal dysfunction [12]. KIM-1 is a more specific marker of kidney damage than serum creatinine blood or blood urea nitrogen [13]. Vaidya et al. observed that the KIM-1 glycoprotein is a biomarker of renal tubular injury in various models of renal injury and is a superior marker to serum creatinine and blood urea nitrogen [13].

The second biomarker analysed in this study is VEGF, known to date mainly for its involvement in the process of angiogenesis [14]. Liu et al. report that VEGF is a key mediator of angiogenesis and vascular permeability, stimulating endothelial cell proliferation and preventing endothelial cell apoptosis [15]. Sharma et al. present that, in addition to its role in the vascular development of the kidney and maintenance of glomerular endothelial integrity, VEGF also has a cytoprotective effect and is responsible for the induction of cellular immunity [16]. It has been shown that a key regulator of VEGF gene expression is oxygen pressure in both *in vitro* and *in vivo* studies. Hypoxia increases the expression of VEGF mRNA. Recent studies emphasise the role of VEGF in preventing apoptosis and vascular regression of endothelial cells and its great influence on renal homeostasis of the kidney. This may provide new therapeutic opportunities in the future [17]. It has been shown that both increased and decreased expression of VEGF within podocytes causes severe renal dysfunction [18]. Overexpression of the VEGF gene causes glomerular hypertrophy and increased proliferation of both endothelial and mesangial cells. These data support the hypothesis that VEGF is involved in maintaining the glomerular barrier and the pathogenesis of proteinuria, suggesting that local activation of VEGF may play a role in glomerulopathies and proteinuria. Inhibition of VEGF secretion in the glomeruli may become a potential target for the treatment of renal diseases, such as diabetic nephropathy and focal segmental glomerulosclerosis. In the long term, VEGF has a negative effect on kidney transplantation, with its expression being negatively correlated with graft survival [19].

The bFGF stimulates the proliferation and migration of endothelial cells in angiogenesis. It plays an important role in maintaining the proper structure of the newly formed vessel through the synthesis of fibronectin, collagen and proteoglycan [20, 21]. It has also been shown that bFGF may accelerate the regeneration process after ischaemic kidney injury [22]. FGF plays an important role in healing and regeneration processes [23]. It supports angiogenesis, chemotaxis and mitogenesis, and stimulates the growth of fibroblasts, myoblasts, osteoblasts, endothelial cells and neuronal cells. Animal studies have shown that direct administration of FGF to the site of a fracture plays a significant role in the efficacy of therapy [24]. FGF has also been shown to induce extracellular proteolysis as well as the proliferation of micro- and macroangiopathic endothelial cells [25]. In addition, a synergistic effect of bFGF and VEGF on microvascular endothelial cells has been documented [26]. FGF and VEGF are potent inducers of angiogenesis in vivo and in vitro [27]. However, bFGF does not increase vascular permeability. The cytokine bFGF in angiogenesis stimulates endothelial cell proliferation and migration of endothelial cells. It plays an important role in maintaining the proper structure of the newly

formed vessel through the synthesis of fibronectin, collagen and proteoglycan. In the period after organ transplantation, there may be increased expression of bFGF, which enhances vascular wall cell proliferation and fibrosis in the transplanted kidney [18].

Conclusions

The study results suggest that the expression of KIM-1, VEGF and bFGF assessed in the transplanted kidney before transplantation is not a significant predictor of the later function of the transplanted kidney. The expression of the bFGF gene correlates with the creatinine levels before and on the first day after transplantation. A statistically significant negative correlation was found between bFGF and serum potassium levels before transplantation and up to one month after transplantation. KIM-1 expression correlated significantly negatively with pre-transplant serum potassium levels. VEGF expression correlated significantly negatively with potassium levels 2 and 24 months after transplantation.

Article information

Ethics statement: *The study was approved by the Ethics Committee of Pomeranian Medical University, Szczecin, Poland (KB-0012/40/14).*

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