European Review for Medical and Pharmacological Sciences 2020; 24: 12794-12801

Expression of syndecan-1, PKC and VEGF in rats with acute kidney injury and correlation between syndecan-1 and renal function

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Abstract. – OBJECTIVE: This study was designed to investigate the expression of syndecan-1 (Sdc-1), protein kinase C (PKC) and vascular endothelial growth factor (VEGF) in rats with acute kidney injury, as well as the association between Sdc-1 and indicators [such as serum creatinine (Scr) and blood urea nitrogen (BUN)] related to renal function.

MATERIALS AND METHODS: A total of 120 clean grade 2-week-old SD rats were selected and randomized into experimental group and control group (n=60). At 12 h (T1), 24 h (T2), 36 h (T3), 48 h (T4) after the model was established, 3 mL blood from abdominal aorta was taken, and Sdc-1, PKC, VEGF, serum creatinine (Scr), urea nitrogen (BUN) and other indicators were detected by Enzyme-Linked Immunosorbent Assay (ELISA).

RESULTS: The expression levels of Sdc-1, PKC and VEGF in the experimental group were increasing from T1 to T4, with statistically significant difference between every two time points ($p<0.05$); the expression levels of Scr and BUN in the experimental group was increasing from T1 to T4, with statistically significant difference between every two time points ($p<0.05$). The level of Sdc-1 in the serum of rats in the experimental group was positively correlated with Scr (r=0.668, $p<0.001$), negatively correlated with BUN (r=0.722, $p<0.001$), and positively correlated with BUN (r=0.722, $p<0.001$); PKC level was positively correlated with Scr (r=0.589, $p<0.001$), BUN (r=0.788, $p<0.001$), and VEGF level was positively correlated with Scr (r=0.666, $p<0.001$), BUN (r=0.784, $p<0.001$).

CONCLUSIONS: As the concentration of syndecan-1 increases gradually, renal dysfunction aggravates accordingly, so syndecan-1 can be used as a marker of acute kidney injury and can be used to judge the degree of kidney injury at an early stage.

Key Words:
Acute kidney injury, Syndecan-1, PKC, VEGF, Related indicators of renal function.

Introduction

Acute kidney injury (AKI), a common disease worldwide, occurs in more than 13 million people every year, 85% of whom live in developing countries[1], while AKI becomes prevalent in developed countries. In hospital patients, the estimated incidence rate is as high as 15%, it is more common in severe patients, and its prevalence rate is estimated to be as high as 60%[2]. This is a serious complication that usually occurs in critically ill patients with devastating consequences[3]. Acute kidney injury is a syndrome characterized by rapid loss of renal excretory function[4]. Although many drugs used to prevent and treat acute kidney injury have shown benefits in preclinical models, it has been proved that no specific drugs show benefits to acute kidney injury in humans[5].

Sdc-1 is a major transmembrane heparan sulfate proteoglycan expressed on the extracellular and luminal surfaces of epithelial cells and syncytiotrophoblasts[6,7]. It has been revealed that it mediates cell adhesion to several extracellular matrix molecules and is an auxiliary receptor for fibroblast growth factor and differentiation-related vascular growth factor[8]. Sdc-1 level was related to subclinical kidney injury and endothelial dysfunction[9]. Protein kinase is a key regulator of various intracellular and extracellular signal transduction pathways, and abnormal phosphorylation can result in progression of various diseases. Therefore, protein kinase has become an important new drug target for small molecule therapy[10]. PKC, an enzyme activated by receptor-mediated inositol phospholipid hydrolysis, transmits various extracellular signals across the cell membrane to regulate many Ca^{2+} dependent processes[11]. PKC-dependent signaling participated in the protection of

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renal ischemic injury[12]. VEGF, mainly called angiogenic factor, is one of the most important factors affecting the growth and survival of vascular endothelium[13]. Low expression of VEGF had a protective effect on kidney[14], acute kidney injury was the most common cause of organ dysfunction in severe patients, and the short-term effect of acute kidney injury was the sharp deterioration of renal function itself[15]. Libório et al[16] demonstrated that endothelial and major glycocalyx injury biomarkers were related to kidney injury in patients with acute kidney injury. According to relevant literature, Scr and BUN could be used to evaluate the renal function of patients[17].

However, there are few references on the expression of Sdc-1, PKC and VEGF and the association between Sdc-1 and renal function indicators in acute kidney injury. Hence, we established rat models of acute kidney injury. In this paper, we tested syndecan-1, PKC and VEGF in patients with acute kidney injury through experiments, in order to provide accurate reference for clinical diagnosis and treatment of them in the future.

Materials and Methods

Animal Data

A total of 120 clean grade 2-week-old SD rats, weighing 180-250 g, were purchased from Guangzhou FOCUSBIO Co., Ltd. They were fed under the environment of temperature (24.00±2.00)°C, humidity (50.00±5.00)%, with natural illumination, free access to food and water. This experiment was approved by the Animal Ethics Committee of Weifang People's Hospital.

Modeling Methods

A total of 120 rats were randomized into an experimental group and a control group (n=60). The rats in the experimental group were anesthetized with phenobarbital, the bilateral renal arteries and renal veins were bluntly separated through a median abdominal incision, and then the bilateral renal arteries were clamped with a non-invasive vascular clamp. After 1 h, the vascular clamp was loosened to restore renal artery blood flow and close the abdomen layer by layer. Rats in the control group only received anesthesia and laparotomy; the renal function indicators, the levels of Scr and BUN after modeling, were observed[18], so as to judge whether the modeling was successful.

Detection Methods

At 12 h (T1), 24 h (T2), 36 h (T3), 48 h (T4) after the model was established (all rats were decapitated at 48 h), 3 mL blood from abdominal aorta was taken respectively. After centrifugation, the supernatant was taken, and the levels of Sdc-1, PKC, VEGF, Scr and BUN were detected by ELISA. Sdc-1 test kit was purchased from Shanghai Yiyan Biotechnology Co., Ltd. (Art. No.: B25952). PKC test kit was purchased from Shanghai Hengfei Biotechnology Co., Ltd. (Art. No.: CSB-E12801r-1). VEGF test kit was purchased from Shanghai Zhenyu Biotechnology Co., Ltd. (Art. No.: CSB-E07352r-1). Scr test kit was purchased from Shanghai Aolu Biotech Co., Ltd.(Art. No.: F8257-B). BUN test kit was purchased from Jiaozuo Lufen Biotechnology Co., Ltd. (Art. No.: LFF-LC-2816). The operation was in strict accordance with the operation requirements provided by the kits.

Observation Indicators

The general conditions of spirit, respiration and diet of rats in each group were observed during the experiment, meanwhile, Sdc-1, PKC, VEGF and renal function indicators, including Scr and BUN were detected for all surviving rats. The changes of T1, T2, T3 and T4 in the above indicators were detected respectively.

Statistical Analysis

SPSS 24.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd.) was used to analyze the data. All graphs were drawn using GraphPad 8 (Shenzhen Qiruitian Software Technology Co., Ltd.) software. All results of this experiment were expressed in the form of (mean±standard deviation). Independent-samples *t*-test was used for comparison between the two groups of normal distribution data, expressed in *t*. Repeated measures analysis of variance and Bonferroni back testing were conducted at multiple time points. The counting data were expressed in percentage and χ^2-test was carried out. Pearson test was used to analyze the relationship between Sdc-1, Scr and BUN in serum of rats in the experimental group. $p<0.05$ was considered to be statistically significant difference.

Results

Modeling Results

Of the 60 modeling rats, 58 were successfully modeled, with a modeling success rate of

Table I. Comparison of the expression levels of Sdc-1 at T1, T2, T3 and T4 in the two groups.

	Syndecan-1 (ng/ml)					
	T1	T2	T3	T4	*t*	*p*
Experimental group	26.96 ± 1.54	28.71 ± 3.31[a]	29.93 ± 1.62[ab]	35.72 ± 1.77[abc]	175	< 0.001
Control group	20.54 ± 1.41	20.77 ± 1.47	20.74 ± 2.12	20.25 ± 1.35	1.785	0.151
t	23.63	16.94	26.39	53.49		
p	< 0.001	< 0.001	< 0.001	< 0.001		

Note: [a] means $p < 0.05$, compared with T1 in the experimental group; [b] means $p < 0.05$, compared with T2 in the experimental group; [c] means $p < 0.05$, compared with T3 in the experimental group.

96.67%. Therefore, there were 58 in the experimental group and 60 in the control group.

Comparison of the Expression Levels of Sdc-1, PKC and VEGF at T1, T2, T3 and T4 in the Two Groups

The expression levels of syndecan-1, PKC and VEGF at T1, T2, T3 and T4 in both groups were compared and observed. The expression levels of syndecan-1, PKC and VEGF in the experimental group were higher at T2 than those at T1, higher at T3 than those at T2, higher at T4 than those at T3, with statistically significant difference ($p<0.05$), and the levels were higher than those in the control group ($p<0.05$), as shown in Tables I, II and III.

Comparison of Related Indicators of Renal Function Between the Two Groups

The expression levels of Scr and BUN at T1, T2, T3 and T4 in the two groups were observed. It was found that the expression levels of Scr and BUN in the experimental group were higher at T2 than those at T1, higher at T3 than those at T2, and higher at T4 than those at T3, with statistically significant difference ($p<0.05$), and the

Table II. Comparison of the expression levels of PKC at T1, T2, T3 and T4 in the two groups.

	PKC (U/L)					
	T1	T2	T3	T4	*t*	*p*
Experimental group	4.05 ± 0.96	6.09 ± 1.39a	13.58 ± 1.69ab	17.08 ± 1.81[abc]	976.6	< 0.001
Control group	3.51 ± 0.73	3.43 ± 1.28	3.55 ± 1.14	3.87 ± 0.69	2.27	0.081
t	3.447	10.82	37.91	52.72		
p	< 0.001	< 0.001	< 0.001	< 0.001		

Note: [a] means $p < 0.05$, compared with T1 in the experimental group; [b] means $p < 0.05$, compared with T2 in the experimental group; [c] means $p < 0.05$, compared with T3 in the experimental group.

Table III. Comparison of the expression levels of VEGF at T1, T2, T3 and T4 in the two groups.

	VEGF (pg/ml)					
	T1	T2	T3	T4	*t*	*p*
Experimental group	0.69 ± 0.08	0.81 ± 0 .14[a]	1.01 ± 0.12[ab]	1.16 ± 0.13[abc]	176.4	< 0.001
Control group	0.56 ± 0.06	0.57 ± 0.04	0.56 ± 0.05	0.58 ± 0.04	2.366	0.072
t	10.01	12.75	26.75	32.99		
p	< 0.001	< 0.001	< 0.001	< 0.001		

Note: [a] means $p < 0.05$, compared with T1 in the experimental group; [b] means $p < 0.05$, compared with T2 in the experimental group; [c] means $p < 0.05$, compared with T3 in the experimental group.

Table IV. Comparison of Scr at T1, T2, T3 and T4

	Scr (υmol/L)					
	T1	T2	T3	T4	*t*	*p*
Experimental group	1.55 ± 0.67	21.34 ± 7.35[a]	25.62 ± 4.53[ab]	31.48 ± 5.14[abc]	385.5	
Control group	0.36 ± 0.25	0.39 ± 0.26	0.41 ± 0.22	0.42 ± 0.19	0.783	
t	12.86	22.07	43.06	46.78		
p	< 0.001	< 0.001	< 0.001	< 0.001		

Note: [a] means $p < 0.05$, compared with T1 in the experimental group; [b] means $p < 0.05$, compared with T2 in the experimental group; [c] means $p < 0.05$, compared with T3 in the experimental group.

Table V. Comparison of BUN at T1, T2, T3 and T4.

	BUN (mmol/L)					
	T1	T2	T3	T4	*t*	*p*
Experimental group	3.58 ± 0.81	30.36 ± 4.79[a]	32.86 ± 5.15[ab]	37.35 ± 4.13[abc]	803	< 0.001
Control group	0.43 ± 0.25	0.47 ± 0.27	0.52 ± 0.24	0.51 ± 0.32	1.374	0.251
t	28.74	48.26	48.59	68.89		
p	< 0.001	< 0.001	< 0.001	< 0.001		

Note: [a] means $p < 0.05$, compared with T1 in the experimental group; [b] means $p < 0.05$, compared with T2 in the experimental group; c means $p < 0.05$, compared with T3 in the experimental group.

levels were higher than those in the control group ($p<0.05$), suggesting that the modeling was successful (Tables IV and V).

Correlation Analysis of Sdc-1 With Scr and BUN in the Experimental Group

Pearson test was used to analyze the correlation between Sdc-1, Scr and BUN in serum of rats in the experimental group, the level of Sdc-1 in serum of rats in the experimental group was positively correlated with Scr (r=0.668, $p<0.001$) and BUN (r=0.722, $p<0.001$), as shown in Table VI, Figure 1 and Figure 2.

Correlation Analysis of PKC With Scr and BUN of Rats in the Experimental Group

Pearson test was used to analyze the correlation between PKC, Scr and BUN in serum of rats in the experimental group, the PKC level in serum of rats in the experimental group was positively correlated with Scr (r=0.589, $p<0.001$) and BUN (r=0.788, $p<0.001$), as shown in Table VII, Figures 3 and 4.

Table VI. Correlation analysis of Sdc-1 with Scr and BUN.

	Scr	BUN')
r	0.668	0.722
95% CI	0.4955-0.7902	0.5706-0.8265
p	<0.001	< 0.001

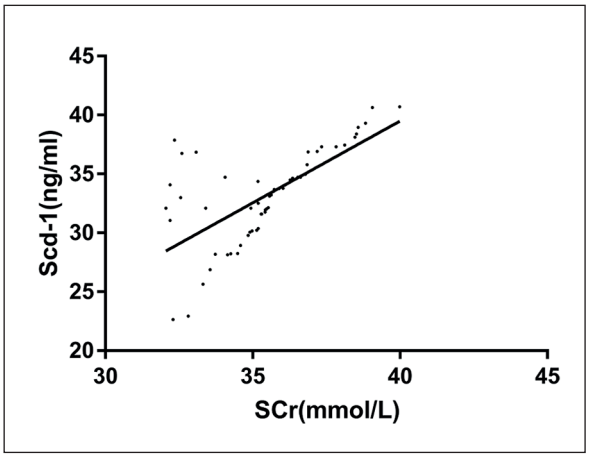

Figure 1. Correlation between the levels of syndecan-1 and Scr in rats with acute kidney injury. Pearson correlation analysis showed that the syndecan-1 level in serum of rats in experimental group was positively correlated with that of Scr (r=0.668, $p<0.001$).

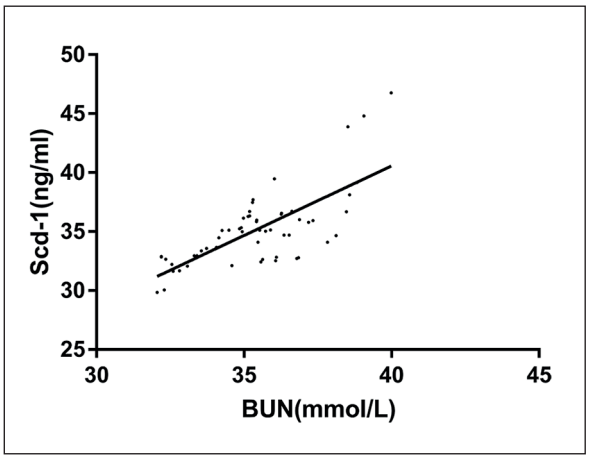

Figure 2. Correlation between the levels of syndecan-1 and BUN in rats with acute kidney injury. According to Pearson correlation analysis, the syndecan-1 level in serum of rats in experimental group was positively correlated with that of BUN (r=0.722, $p<0.001$).

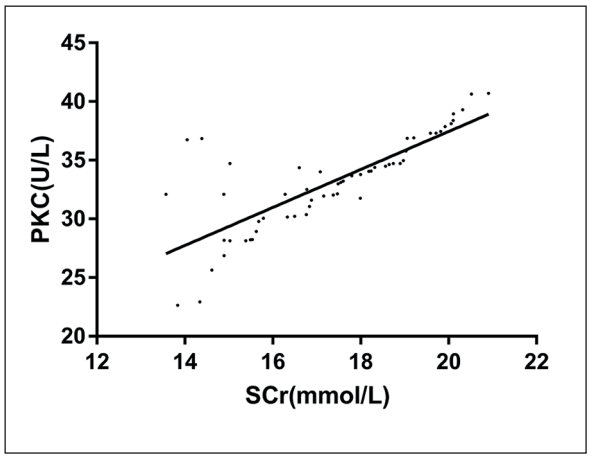

Figure 3. Correlation between the levels of syndecan-1 and BUN in rats with acute kidney injury. According to Pearson correlation analysis, the syndecan-1 level in serum of rats in experimental group was positively correlated with that of BUN (r=0.722, $p<0.001$).

Correlation Analysis of VEGF With Scr and BUN of Rats in the Experimental Group

Pearson test was used to analyze the correlation between VEGF, Scr and BUN in serum of rats in the experimental group, the VEGF level in serum of rats in the experimental group was positively correlated with Scr (r=0.666, $p<0.001$) and BUN (r=0.784, $p<0.001$), as shown in Table VIII, Figures 5 and 6.

Discussion

Acute kidney injury is the most common cause of organ dysfunction in severe patients; its incidence rate of patients in Intensive Care Unit is about 34%, and the observed hospital mortality is as high as 62%[19], which is a syndrome characterized by rapid deterioration of renal function (hours to days)[20]. Acute kidney injury is one of the increasingly high-risk diseases in the clinic, and the condition deteriorates extremely rapidly. Once it is not effectively intervened in time, it will pose a serious threat to the life of patients. At present, the clinical evaluation of the occurrence of acute kidney injury has extremely high limitations, and it can be confirmed by multiple examinations such as blood, imaging or renal tissue biopsy. The most evident indicators of renal injury, SCr and BUN, have also been found to gradually decrease the specificity of the response to renal injury. Therefore, searching for more novel, sensitive and accurate indicators of kidney injury is of great significance for clinical judgment of the occurrence of kidney injury in the future. This study, by explor-

Table VII. Correlation analysis of PKC with Scr and BUN.

	Scr	BUN')
r	0.589	0.788
95% CI	0.3912-0.7361	0.6655-0.8695
p	< 0.001	< 0.001

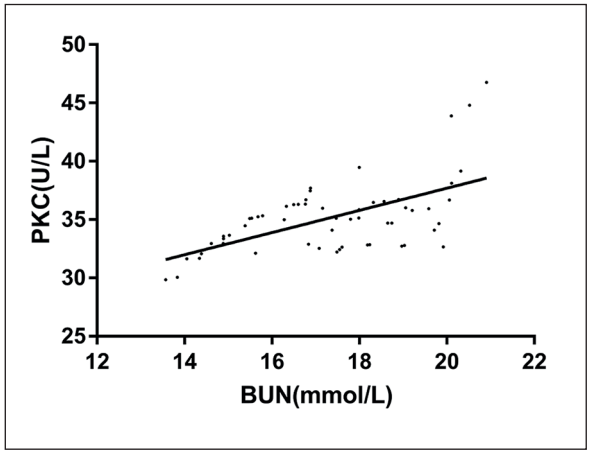

Figure 4. Correlation between the levels of PKC and BUN in rats with acute kidney injury. Pearson correlation analysis indicated that PKC and BUN in serum of rats in experimental group were positively correlated (r=0.788, $p<0.001$).

Table VIII. Correlation analysis of VEGF, Scr and BUN.

	Scr	BUN')
r	0.666	0.784
95% CI	0.4922-0.7885	0.6598-0.867
p	< 0.001	< 0.001

ing the clinical significance of Sdc-1 and VEGF in acute kidney injury, can provide a reliable clinical theoretical basis for the future clinical response to acute kidney injury.

Sdc-1, a kind of heparan sulfate proteoglycan on cell surface, regulates a variety of cell behaviors, including adhesion, proliferation, movement, intracellular signals, growth factors and macromolecular cell surface binding and intracellular internalization, angiogenesis, lipid metabolism, wound healing, regulation of leukocyte migration and endothelial response[21]. BUN and Scr are important indicators of the severity of renal damage, which are currently the most commonly used detection indicators for renal function in clinical and animal studies[22,23]. It was reported that PKC played an important role in the occurrence and progression of diabetic nephropathy; the synthesis of vascular endothelial growth factor induced by high glucose was blocked by PKC inhibition or downregulation, which indicated that PKC pathway participated in the production of vascular endothelial growth factor in mesangial cells, so PKC inhibitors might be helpful to prevent the excessive production of vascular endothelial growth factor in diabetic patients[24,25].

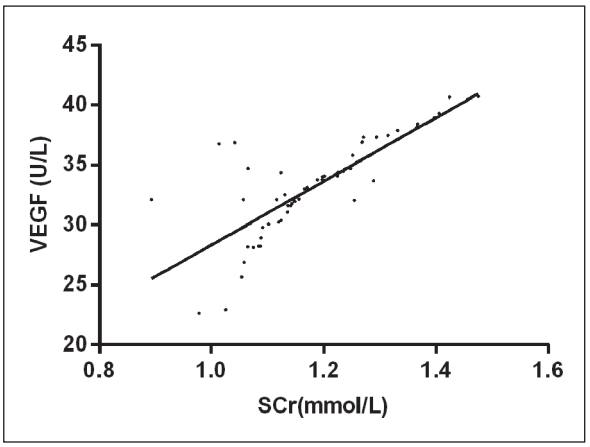

Figure 5. Correlation between the levels of VEGF and Scr in rats with acute kidney injury. Pearson correlation analysis displayed that the VEGF level in serum of rats in experimental group was positively correlated with that of Scr (r=0.666, $p<0.001$).

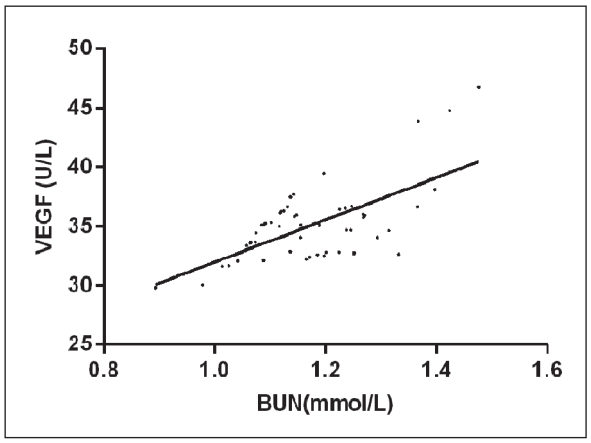

Figure 6. Correlation between the levels of VEGF and BUN in rats with acute kidney injury. Pearson correlation analysis displayed that VEGF and BUN in serum of rats in experimental group were positively correlated (r=0.784, $p<0.001$).

VEGF is an effective cytokine for promoting vascular endothelial growth and plays a key role in maintaining glomerular function[26]. VEGF supplementation had a protective effect in cases of thrombotic microvascular disease, ischemia reperfusion and chronic renal vascular disease[27]. Moreover, blocking VEGF had a protective effect on the early kidney injury of diabetic rats[28], and studies[29] showed that VEGF and syndecan-1 might exert in the stimulation of myeloma cell growth and angiogenesis. In addition, non-matrix metalloproteinase is the cause of syndecan-1 shedding[30]. This study aimed to explore the value of Sdc-1 in patients with acute kidney injury related to renal function, through establishing rat models with acute kidney injury and detecting syndecan-1, PKC, VEGF and related indicators of renal function.

The experimental results showed that the expression levels of Sdc-1, PKC and VEGF in the experimental group were higher at T2 than those at T1, higher at T3 than those at T2, and higher at T4 than those at T3, with statistically significant difference ($p<0.05$), higher than those in the control group ($p<0.05$), with an upward trend as time went by. The expression levels of Scr and BUN in the experimental group were higher than those in the control group at T1, T2, T3 and T4 ($p<0.05$), with an upward trend as time went by, suggesting successful modeling. In this study, the expression of Sdc-1 increased. de Melo Bezerra Cavalcante et al[31] discovered that the expression level of Sdc-1 increased in acute kidney injury caused by pediatric cardiac sur-

gery, which was approximately consistent with the results of this study. However, Guo et al[32] found that VEGF was an attractive target for the treatment of hypoxic/ischemic brain damage. We speculated that VEGF might also have the effect of improving hypoxia and ischemia in acute kidney injury. Pearson test was used to analyze the correlation between Sdc-1, PKC, VEGF, Scr and BUN in serum of rats in the experimental group, the level of Sdc-1 in serum of rats in the experimental group was positively correlated with Scr ($r=0.668$, $p<0.001$), negatively correlated with BUN ($r=0.722$, $p<0.001$), and positively correlated with BUN ($r=0.722$, $p<0.001$). PKC level was positively correlated with Scr ($r=0.589$, $p<0.001$), BUN ($r=0.788$, $p<0.001$), VEGF level was positively correlated with Scr ($r=0.666$, $p<0.001$), BUN ($r=0.784$, $p<0.001$), suggesting that the increase of the levels of Sdc-1, PKC and VEGF would lead to aggravation of renal dysfunction.

Nevertheless, there are still some limitations in our research. Further research is needed on the mechanism of Sdc-1 on acute kidney injury, and there are always some differences between animal models and human bodies. We will carry out human body experiments as soon as possible and continuously improve our experiments to obtain the best experimental results.

Conclusions

To sum up, the expression of Sdc-1 in acute kidney injury was positively correlated with the expression of related indicators of renal function, suggesting that with the concentration of Sdc-1 gradually increasing, renal dysfunction aggravated accordingly, so Sdc-1 could be used as a marker of acute kidney injury and could be used to judge the degree of kidney injury at an early stage.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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