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Clinical Significance of Sonic Hedgehog in Renal Interstitial Fibrosis of Chronic Kidney Disease Patients

Yanting Zhu, Xiaoming Wang, Yan Sun, Qiong Wang, Xiaohui Yan*

Department of Nephropathy, Shaanxi Provincial People' s Hospital, Xi' an 710068, Shaanxi, China

Author to whom correspondence should be addressed.

Abstract: *Background*: Sonic hedgehog (SHH) has been found to be involved in chronic kidney disease (CKD) development. *Aims*: This study aims to explore the clinical significance of SHH in renal interstitial fibrosis (RIF) of CKD patients. *Methods*: SHH serum levels were determined using enzyme-linked immunosorbent assays. Expressions of SHH, TGF-β and CTGF in kidney biopsy specimens of CKD patients were measured by immunohistochemistry staining. *Results*: Serum levels of SHH were significantly higher in stage 3–4 and stage 5 of CKD patients than that in healthy controls. SHH levels were positively correlated with Scr, BUN and UA levels; negatively correlated with HGB and eGFR in CKD patients. SHH was the risk factor for DKD. In addition, The expression of SHH was significantly increased in stage 3–4 patients compared to stage 1–2 patients, and increased in severe interstitial fibrosis group than that in the mild interstitial fibrosis group. SHH expression was positively correlated with renal interstitial fibrosis score and profibrotic factors (TGF-β and CTGF) in CKD patients. *Conclusions*: SHH might serve as a potential biomarker for CKD and mediate the pathogenesis of RIF in CKD patients.

Keywords: Chronic kidney disease; Renal interstitial fibrosis; Sonic hedgehog; Serum biomarker; Kidney biopsy specimens

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1. Background

Chronic kidney disease (CKD) is a worldwide public health issue characterized by an irreversible damage of renal parenchyma leading to gradually progress in deterioration of renal function, eventually resulting in the occurrence of end-stage renal failure (ESRD) and the acceleration of cardiovascular disease [1–3]. Renal interstitial fibrosis (RIF) including massive fibrosis in renal tubules and tubulointerstitium is a key pathological feature of CKD, which is majorly caused by renal tubule injury [4–6]. In response to injury, tubular epithelial cells (TECs) play important roles

in renal repair, which induce the production of various profibrotic factors, such as transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF), which drive interstitial fibrosis [4,7,8].

The hedgehog (HH) signaling pathway is an evolutionarily conserved pathway that regulates organ morphogenesis in the mammalian embryo and plays a decisive role in tissue homeostasis [9]. Three HH ligands are found in mice and humans: sonic hedgehog (SHH), desert hedgehog (DHH), and Indian hedgehog (IHH) ligands [10]. These secreted ligands bind to the transmembrane receptor Ptch, thereby freeing the G-protein coupled transmembrane protein SMO, which is sequestered by Ptch in the absence of ligand [10]. Accumulated SMO active glioma-associated oncogene homolog 1 (GLI1) transcriptional factors, which regulate cell proliferation, differentiation and invasion [11–13]. SHH is a secreted protein mainly produced by renal tubular epithelium. The functionality of SHH in the development of CKD has been extensively studied [14–16]. Studies have indicated that overexpression of SHH promoted fibroblast proliferation and extracellular matrix deposition, thereby leading to kidney fibrosis [16,17]. However, the serum levels of SHH and the expression of SHH in kidney tissues of CKD patients have not yet been investigated. Therefore, this study was conducted to explore the effect of SHH on RIF development and the utility of SHH as a potential biomarker for CKD.

2. Methods

2.1. Study population

Non-dialysis CKD patients, diagnosed according to the kidney disease: Improving Global Outcomes (KDIGO) guidelines, were admitted to the center of nephropathy and dialysis of Shaanxi Provincial People's Hospital (Xi'an, Shaanxi, China) from June 2023 to June 2024. Patients with severe liver disease, severe infection, immune deficiency, malignant tumors or acute kidney injury were excluded. 73 CKD patients met the inclusion criteria. Patients were divided into three groups according to the estimated glomerular filtration rate (eGFR): mild CKD patients (CKD stage 1–2 group, n = 24), severe CKD patients (CKD stage 3–4 group, n = 26) and patients with ESRD (CKD stage 5 group, n = 23). 21 patients received kidney biopsy in which 13 patients were from CKD stage 1–2 group, the others were in CKD stage 3–4 group. 21 patients with biopsy-proven CKD were also divided into two groups: mild interstitial fibrosis (interstitial fibrosis score < 25%, n = 15) and severe interstitial fibrosis (interstitial fibrosis score ≥ 25%, n = 6). 20 healthy controls were included in the analysis. The present study was approved by the ethical committee for human investigation of Shaanxi Provincial People's Hospital and was conducted according to the Declaration of Helsinki. Informed consent was obtained from all participants.

2.2. Measurements of clinical parameters

Detailed clinical and demographic data were collected on admission. The basic information, including gender, age, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained from each patient. The following clinical laboratory measurements were performed for each patient: serum creatinine (Scr), blood urea nitrogen (BUN), uric acid (UA), albumin (ALB), triglyceride (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and hemoglobin (HGB) at the time of enrollment. 24-hour urine protein was measured according to the standard methods in the routine clinical laboratory. The eGFR was calculated according to the modified MDRD formula: $eGFR = 186 \times Scr^{-1.154} \times Age^{-0.203} \times$ gender (1 if male, 0.742 if female).

2.3. Processing of blood and tissue samples

Peripheral blood was collected by venipuncture from all patients and stored at 4 ℃ within 24 hours of hospital admission. Blood sample were centrifuged at 3,000g at 4 ℃ for 15 minutes, and then serum was

collected and stored at -80 ℃.

Kidney biopsy specimens were obtained from 21 CKD patients. The renal specimens were immersed with 4% paraformaldehyde for 24 h at room temperature, and then embedded in paraffin wax. Paraffin-embedded tissue was cut at a thickness of 5 μm and mounted on glass slides.

2.4. Enzyme-linked immunosorbent assays

The serum levels of SHH were measured using enzyme-linked immunosorbent assay (ELISA) kits (Xinbosheng, Inc., Shenzhen, China) according to the manufacturer's instructions. The lower detectable limit of the SHH using these kits were 46.88 pg/mL. 100 μL serum sample from each patient was added to the testing plates and then incubated for 90 min at 37 ℃. Subsequently, serum samples were removed and then 100 μL horse-radish-peroxidase-(HRP)-conjugated specific antibody was added for 60 min at 37 ℃. After being washed 3 times, 100 μL enzyme binding work solution was added for 30 min at 37 ℃. Wells were then washed 5 times. The substrate solution was added for 15 min at 37 ℃. Finally, reaction was terminated by the addition of terminating solution, and the OD value was measured spectrophotometrically at a wave length of 450 nm. Each sample was run in duplicate and compared with a standard curve.

2.5. Histological and immunohistochemical staining

Histological and immunohistochemical staining were performed on paraffin-embedded, 3-μm-thick tissue sections. Changes in renal morphology were assessed by hematoxylin and eosin (HE), periodic acid-Schiff (PAS) and Masson's staining as previously described [18,19]. To assess the expressions of SHH, TGF-β and CTGF, immunohistochemistry staining was performed as described. The paraffin-embedded tissue sections were deparaffinized and rehydrated, washed with PBS, incubated in 3% hydrogen peroxide for 10min, and then blocked with buffered normal goat serum for 30 min at room temperature. Thereafter, the slides were incubated with specific primary antibodies against SHH (Abcam, Cambridge, UK; 1:2000 dilution), TGF-β (Saiweier, Wuhan, China; 1:500 dilution) and CTGF (Saiweier, Wuhan, China; 1:500 dilution) at 4 ℃ overnight. After being washed with PBS, sections were incubated with horseradish peroxidase-conjugated secondary antibody (Sigma-Aldrich; 1:2000 dilution) at room temperature for 1 h. Finally, the sections were incubated with diaminobenzidine (DAB), dehydrated, coverslipped and observed using a light microscope (Olympus, Japan). The integrated optical density (IOD) was measured using Image Pro Plus 6.0 software.

2.6. Statistical analysis

SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Normally distributed data were presented as mean ± SD and non-normally distributed data were expressed as median range. Differences between two groups for quantitative data and qualitative data were compared using a *t* test and chi-square test, respectively. Comparisons of normally distributed data in 3 or more groups were analyzed using one-way ANOVA. Correlations were examined using Pearson's correlation analysis. Binary regression analysis was used to determine the influence factors of the presence of CKD. $p < 0.05$ was considered to represent significant differences between groups.

3. Results

3.1. Characteristics of study populations

The basic characteristics of all patients and the results of biochemical analyses within the groups were

displayed in **Table 1**. 73 CKD patients (stage 1–2, n = 24; stage 3–4, n = 26; stage 5, n = 23) were evaluated (47 males, 26 females). The median age of patients was 53.74 years. Scr, BUN and UA levels in stage 5 CKD patients were higher than those in stage 1–2 and stage 3–4 patients as well as healthy controls ($p < 0.01$). SBP was also extremely higher in stage 5 CKD patients ($p < 0.01$). HGB and eGFR were significantly decreased in stage 5 CKD patients compared to stage 1–2 and stage 3–4 patients as well as healthy controls ($p < 0.05$). HDL-C was also significantly lower in stage 5 CKD patients compared to stage 1–2 patients and healthy controls ($p < 0.01$). Decreased ALB and increased 24-hour urine protein were evident in all groups of CKD patients in comparison with healthy subjects ($p < 0.05$).

Table 1. The basic characteristics and clinical parameters of the study subjects

Parameter	Control group (n = 20)	All patients (n = 73)	Stage 1–2 CKD (n = 24)	Stage 3–4 CKD (n = 26)	Stage 5 CKD (n = 23)
Age (years)	50.15 ± 13.00	53.74 ± 17.24	47.38 ± 17.03	62.08 ± 13.79	50.96 ± 17.86
Sex (Male/Female)	11/9	47/26	13/11	20/6	14/9
SBP (mmHg)	124.50 ± 17.69	139.78 ± 21.67*	126.92 ± 15.48	144.08 ± 20.38	148.35 ± 23.13
DBP (mmHg)	78.20 ± 12.80	82.16 ± 12.47	77.21 ± 9.78	83.00 ± 13.64	86.39 ± 12.28
Scr (μmol/L)	53.48 ± 13.12	354.19 ± 354.88*	63.98 ± 15.69	266.33 ± 109.68	756.33 ± 358.01
BUN (mmol/L)	5.16 ± 1.40	15.27 ± 10.56*	5.08 ± 1.53	13.98 ± 5.11	27.35 ± 8.06
UA (μmol/L)	296.21 ± 80.89	439.41 ± 122.17*	340.66 ± 74.28	454.51 ± 107.53	526.02 ± 105.11
ALB (g/L)	40.70 ± 5.34	32.08 ± 7.21*	29.73 ± 8.82	34.01 ± 5.75	32.46 ± 6.26
TG (mmol/L)	2.07 ± 2.20	1.83 ± 1.75	2.26 ± 1.85	1.63 ± 0.91	1.58 ± 1.38
TC (mmol/L)	4.64 ± 1.01	4.40 ± 2.11	5.58 ± 2.98	3.78 ±1.16	3.73 ± 0.84
HDL-C (mmol/L)	1.22 ± 0.31	1.07 ± 0.35	1.27 ± 0.43	1.00 ± 0.26	0.92 ± 0.20
LDL-C (mmol/L)	2.45 ± 0.71	2.40 ± 1.31	3.02 ± 1.83	2.02 ± 0.87	2.11 ± 0.61
HGB (g/L)	139.15 ± 16.99	111.63 ± 26.53*	137.33 ± 19.73	106.80 ± 19.97	90.04 ± 14.00
eGFR (mL/min/1.73m^2)	141.58 ± 29.98	51.72 ± 58.59*	119.01 ± 57.96	28.74 ± 9.63	7.50 ± 2.79

Data are presented as mean ± SD or number. SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; ALB, albumin; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; HGB, hemoglobin; eGFR, estimated glomerular filtration rate.

3.2. Concentrations of serum SHH

The differences of serum SHH levels in CKD patients and healthy controls are shown in **Table 2** and **Figure 1**.

Table 2. Concentrations of serum SHH

Parameter	Control group (n = 20)	All patients (n = 73)	Stage 1–2 CKD (n = 24)	Stage 3–4 CKD (n = 26)	Stage 5 CKD (n = 23)
SHH (ng/mL)	0.43 ± 0.19	2.73 ± 2.12*	0.81 ± 0.44	2.65 ± 0.96	4.82 ± 2.20

Data are presented as mean ± SD.

Figure 1 indicates that the levels of SHH were significantly higher in stage 3–4 and stage 5 CKD patients than that in healthy controls (both $p < 0.01$). Patients in stage 5 had significantly higher SHH levels

than the other two groups of CKD patients (both $p < 0.01$). The levels of SHH were extremely elevated in stage 3–4 patients compared to stage 1–2 patients (both $p < 0.05$). Whereas, there was no significant difference in the serum SHH levels between stage 1–2 CKD patients and healthy controls ($p = 0.495$).

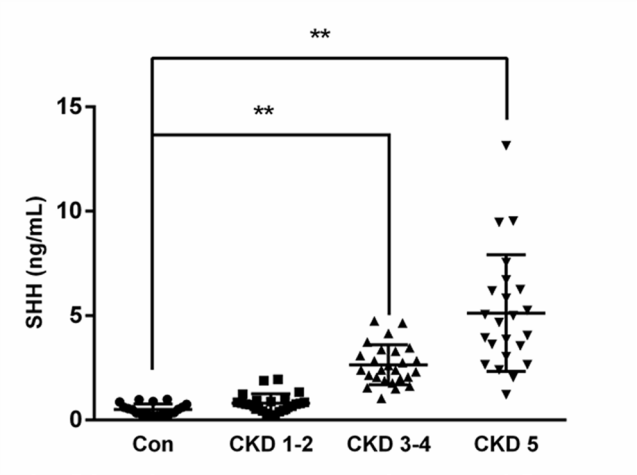

Figure 1. Concentrations of serum SHH in CKD patients and healthy controls.

The serum levels of SHH are increased in stage 3–4 and stage 5 of CKD patients than that in healthy controls. Values of SHH were expressed as mean ± SD. $^{**}p < 0.01$ versus healthy controls.

3.3. Correlation between the levels of SHH and clinical parameters among CKD patients

The correlations between the changes of SHH levels and clinical parameters among the studied CKD patients are shown in **Table 3**. The analyses indicated positive correlations between the levels of SHH and Scr, BUN and UA levels in CKD patients (all $p < 0.01$). In addition, SHH levels were negatively correlated with HGB and eGFR (both $p < 0.01$).

Table 3. Correlation between SHH levels and levels of clinical parameters among CKD patients

Parameter	SHH (ng/mL) among the studied CKD patients (n = 73)	
	R	*p* value
SBP (mmHg)	0.20	0.085
DBP (mmHg)	0.16	0.171
Scr (μmol/L)	0.57	< 0.001
BUN (mmol/L)	0.66	< 0.001
UA (μmol/L)	0.44	< 0.001
ALB (g/L)	0.11	0.376
TG (mmol/L)	-0.25	0.043
TC (mmol/L)	-0.34	0.005
HDL-C (mmol/L)	-0.35	0.004
LDL-C (mmol/L)	-0.30	0.016
HGB (g/L)	-0.62	< 0.001
24-h urine protein (g/24h)	-0.19	0.135
eGFR (ml/min)	-0.60	< 0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; ALB, albumin; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; HGB, hemoglobin; eGFR, estimated glomerular filtration rate.

3.4. Influence factor in the presence of CKD

Binary regression analysis showed that SHH was the risk factor of CKD ($p = 0.029$); while, ALB and eGFR were found to be the protective factor of CKD (both $p < 0.05$) (**Table 4**).

Table 4. Influence factor in the presence of CKD

Parameter	B	SE	Walds	*p*	OR
SHH	0.325	0.894	4.777	0.029	1.421
ALB	-0.605	0.242	6.262	0.012	0.546
eGFR	-0.039	0.019	4.259	0.039	0.961

ALB, albumin; eGFR, estimated glomerular filtration rate. $p < 0.05$ was considered significant.

3.5. Expression and localization of SHH in kidney biopsy specimens of CKD patients

Figure 2 shows that the protein of SHH was mainly expressed in cytoplasmic of renal tubular epithelial cells. As shown in **Figure 2**, the expression of SHH was significantly increased in stage 3–4 patients compared to stage 1–2 patients ($p > 0.05$).

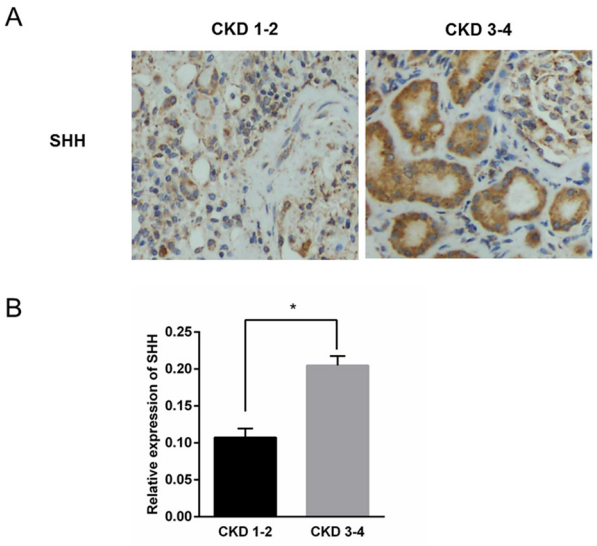

Figure 2. Expression and localization of SHH in kidney biopsy specimens of CKD patients

(A) Representative images of immunohistochemistry staining are shown (n = 4 per group). (B) The expression of SHH is increased in renal biopsy tissues from stage 3–4 CKD patients compared with stage 1–2 patients. Values of SHH was expressed as mean ± SD.*$p < 0.05$ versus stage 1–2 CKD patients.

3.6. Expression of SHH is correlated with renal interstitial fibrosis in kidney biopsy specimens of CKD patients

Figure 3A shows the level of tubulointerstitial fibrosis and ECM deposition in mild and severe interstitial fibrosis groups by HE, PAS and Masson's staining. As depicted in **Figure 3B**, patients in severe interstitial fibrosis group had extremely higher expression of SHH than in the mild interstitial fibrosis group. Similarly, TGF-β and CTGF proteins were increased in severe interstitial fibrosis group compared with mild interstitial fibrosis group. Correlation analysis showed a significant association between SHH expression and renal interstitial fibrosis score ($p < 0.001$) (**Figure 3C**). **Figure 3D** and **3E** showed that there was a positive association between SHH protein expression and TGF-β, CTGF expressions (both $p < 0.001$).

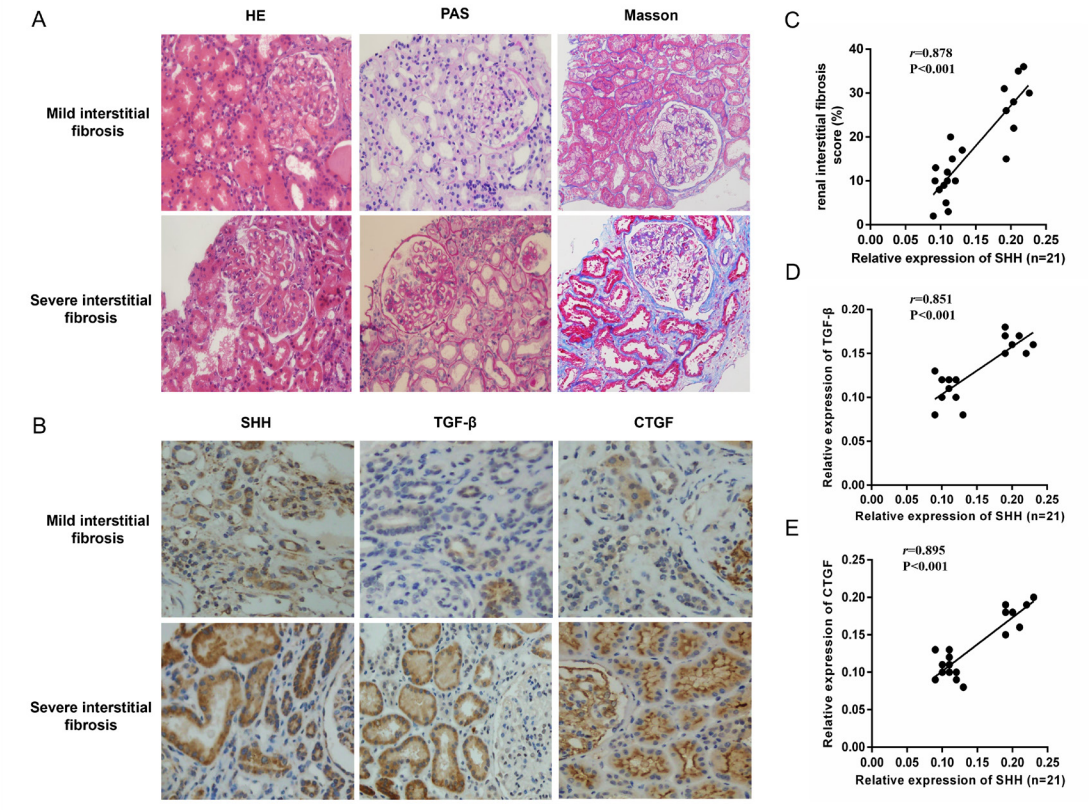

Figure 3. Expression of SHH is correlated with renal interstitial fibrosis in kidney biopsy specimens of CKD patients

(A) Representative images of HE, PAS and Masson staining are shown. (B) Representative images of immunohistochemistry staining are shown (n = 4 per group). The expression of SHH, TGF-β and CTGF are increased in renal biopsy tissues from severe interstitial fibrosis patients (renal interstitial fibrosis score ≥ 25%) compared with mild interstitial fibrosis patients (renal interstitial fibrosis score < 25%). Correlation of the expression of SHH and renal interstitial fibrosis score (C) as well as TGF-β (D), CTGF (E) in CKD patients.

4. Discussion

CKD is a common disorder characterized by a permanent damage of kidney structure and deterioration

of renal function, eventually resulting in the occurrence of ESRD and complications [1–3]. RIF including massive fibrosis in renal tubules and tubulointerstitium plays a critical role in CKD development. TECs often localize at the epicenter of kidney injury and are especially vulnerable to damage [20]. In response to severe or recurrent injury, TECs undergo a variety of maladaptive changes in structure and phenotype, such as epithelial-mesenchymal transition (EMT); and induce the production of various profibrotic factors, such as CTGF, TGF-β and SHH [4,7,8,21–23].

HH signaling pathway has important roles in mammalian development that regulates tissue patterning, cell growth and differentiation [9,11,12]. SHH a secreted protein is mainly produced by renal tubular epithelium and associated with kidney development and tissue repair after various insults [24]. While, the expression of SHH is largely silenced in healthy adult kidney. Activation of SHH signaling pathway has been found to mediate the pathogenesis of CKD, in which SHH targets interstitial fibroblasts, thereby mediating a dynamic epithelial-mesenchymal communication (EMC) [14–16,24,25]. It has been shown that the expression of SHH is up-regulated in ischemia reperfusion injury (IRI) and unilateral ureteral obstruction (UUO) CKD mouse models [14,16,25]. SHH has been shown to be also over-expressed in renal tubular epithelium in kidney biopsy specimens of CKD patients, regardless of the initial etiologies [16]. Further study has shown that overexpression of SHH promotes fibroblast proliferation and activation, extracellular matrix deposition in UUO mouse model [15]. However, knockout of SHH in mice or pharmacologic inhibition of SHH reduces fibrotic lesions after kidney injury in IRI model [26].

This present study shows that serum SHH levels in stage 3–4 and stage 5 CKD patients were higher than that in the healthy controls. The serum levels of SHH were gradually increased accompanied with progression in deterioration of renal function. SHH levels had a positive correlation with Scr, BUN and UA levels; while negatively correlated with HGB and eGFR in CKD patients. Binary regression analysis showed that SHH was the risk factor of DKD. These findings suggested that SHH may serve as a specific serum biomarker to reflect the damage of kidney and might be as a supplement to diagnose CKD. In addition, we found that the expression of SHH was mainly expressed in cytoplasmic of renal tubular epithelial cells. SHH expression was significantly increased in stage 3–4 patients compared to stage 1–2 patients. Furthermore, patients in severe interstitial fibrosis group had extremely higher expression of SHH than in the mild interstitial fibrosis group. The expression of SHH was positively correlated with renal interstitial fibrosis score and profibrotic factors (TGF-β and CTGF) in CKD patients. The above results indicated that SHH might be involved in the pathogenesis of RIF of CKD and might be an efficient target for CKD prevention and treatment.

5. Conclusion

In conclusion, this present study observed that serum levels of SHH are increased in CKD patients and serum SHH is an independent risk factor of DKD. Furthermore, SHH expression in kidney biopsy specimens is increased in severe interstitial fibrosis group than that in the mild interstitial fibrosis group, which is positively associated with RIF score and profibrotic factors (TGF-β and CTGF) in CKD patients, suggesting that SHH might serve as a potential biomarker for CKD and mediate the pathogenesis of RIF in CKD patients.

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Disclosure statement

The authors declare no conflict of interest.

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