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Urology Research

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

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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 $\geq 25\%$, $n = 6$). 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: $eGFR = 186 \times Scr^{-1.154} \times Age^{-0.203} \times \text{gender}$ (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 °C within 24 hours of hospital admission. Blood sample were centrifuged at 3,000g at 4 °C for 15 minutes, and then serum was

collected and stored at -80 °C.

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 °C. Subsequently, serum samples were removed and then 100 µL horse-radish-peroxidase-(HRP)-conjugated specific antibody was added for 60 min at 37 °C. After being washed 3 times, 100 µL enzyme binding work solution was added for 30 min at 37 °C. Wells were then washed 5 times. The substrate solution was added for 15 min at 37 °C. 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 °C 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 ($p = 0.495$).

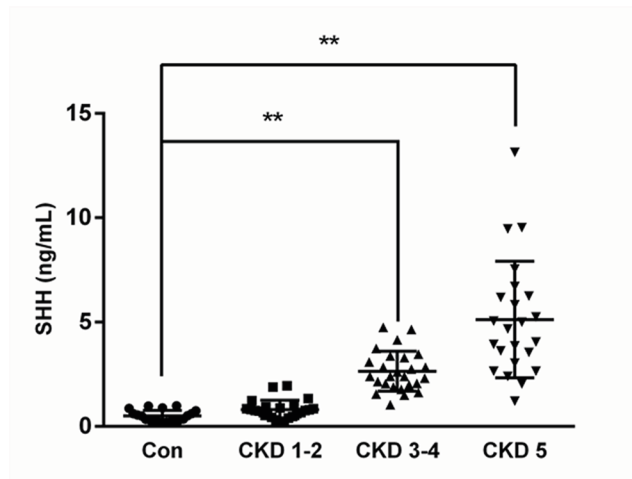


Figure 1. Concentrations of serum SHH in CKD patients and healthy controls.

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 $\pm$ 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	<i>p</i> value
SBP (mmHg)	0.20	0.085
DBP (mmHg)	0.16	0.171
Scr (μ mol/L)	0.57	< 0.001
BUN (mmol/L)	0.66	< 0.001
UA (μ mol/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	<i>p</i>	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 ($p > 0.05$).

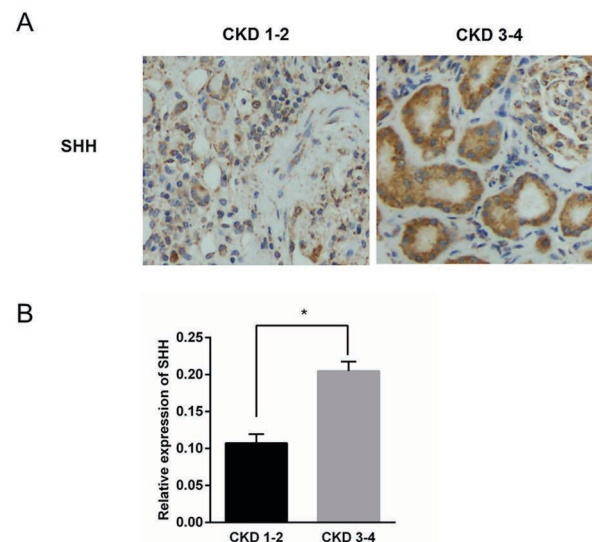


Figure 2. Expression and localization of SHH in kidney biopsy specimens of CKD patients

(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 $\pm$ 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 $p < 0.001$).

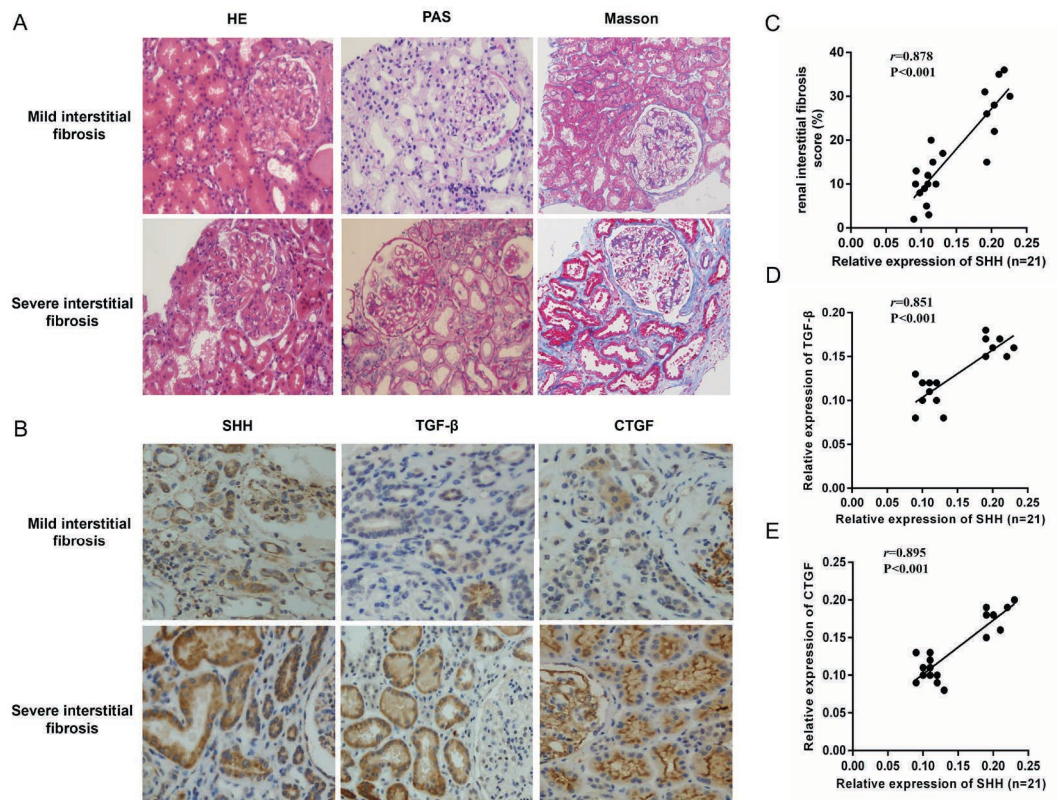


Figure 3. Expression of SHH is correlated with renal interstitial fibrosis in kidney biopsy specimens of CKD patients

(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 $\geq 25\%$) 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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Research Progress on the Mechanism of LncRNA GAS5 in Regulating the Radiosensitivity of Prostate Cancer

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Abstract: Prostate cancer is a prevalent malignant tumor in the male urogenital system. Radiotherapy, which uses high-energy radiation to kill cancer cells, serves as a cornerstone for local advanced and postoperative adjuvant treatment, yet tumor radioresistance, when cancer cells survive and adapt to radiation, significantly limits therapeutic efficacy. Long non-coding RNA (lncRNA) GAS5, a critical tumor-suppressive transcript, is commonly under expressed in prostate cancer and positively regulates radiosensitivity (the tendency of cells to be destroyed by radiation) through multiple mechanisms, including competing endogenous RNA (ceRNA, a process where RNAs regulate each other's expression by competing for shared microRNAs) regulation, DNA damage repair, cell cycle arrest, induction of apoptosis (programmed cell death), and interactions with signaling pathways. This review systematically summarizes the structural and functional characteristics of GAS5, its expression patterns in prostate cancer, and elucidates the molecular mechanisms underlying its regulation of radiosensitivity. Additionally, it explores clinical application prospects and existing challenges, providing theoretical evidence and novel insights for enhancing precision radiotherapy in prostate cancer.

Keywords: Long non-coding RNA; GAS5; Prostate cancer; Radiosensitivity; Molecular mechanism; ceRNA; DNA damage repair

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1. Introduction

Prostate cancer (PCa) is among the most prevalent malignant tumors in men worldwide. In China, its incidence is steadily rising due to population aging and increased screening, posing a significant threat to male health ^[1]. Radiotherapy plays a pivotal role across localized, locally advanced, and metastatic PCa stages. It effectively controls local lesions, reduces the risk of recurrence, and prolongs survival ^[2]. However, approximately 30–50% of patients develop primary or acquired radioresistance in clinical practice. This leads to local treatment failure, distant metastasis, and therapeutic failure, a critical challenge in prostate cancer

radiotherapy. Long non-coding RNAs (lncRNAs) are transcripts exceeding 200 nucleotides in length that do not encode or only encode short peptides. They are extensively involved in tumor proliferation, invasion, metastasis, and treatment resistance through epigenetic, transcriptional, and post-transcriptional regulation, as well as interactions with signaling pathways. Growth arrest-specific transcript 5 (GAS5) is located on human chromosome 1q25.1 and was initially identified for its high expression in growth-arrested cells. It functions as a tumor suppressor in various malignancies, including breast, lung, gastric, and prostate cancers. Its expression levels are closely correlated with tumor grade, stage, and prognosis ^[3]. Recent studies confirm that GAS5 is significantly under expressed in prostate cancer tissues and cell lines. Overexpression of GAS5 markedly inhibits proliferation, promotes apoptosis, and enhances radiotherapy-induced cytotoxicity. This positions it as a promising radiosensitizing target ^[4]. Current research has elucidated multiple key pathways through which GAS5 regulates radiosensitivity in prostate cancer. These include ceRNA networks, DNA damage response, cell cycle checkpoints, apoptotic pathways, and classical signaling axes. This review synthesizes recent domestic and international advances. It systematically outlines the molecular mechanisms by which GAS5 modulates radiosensitivity in prostate cancer and summarizes foundational and translational research findings, which inform the development of novel radiosensitization strategies.

2. Biological characteristics of LncRNA GAS5 and its expression pattern in prostate cancer

2.1. Gene structure and functional characteristics of GAS5

The GAS5 gene spans approximately 630 base pairs (bp) and comprises 12 exons. It generates multiple splice variants through transcription. Its core functional region contains a sequence highly homologous to the DNA-binding domain of the glucocorticoid receptor (GR). This enables competitive binding to GR and subsequent inhibition of its transcriptional activity. This mechanism regulates the expression of downstream genes involved in metabolism and proliferation ^[5]. GAS5 is widely expressed in normal tissues and is upregulated under conditions such as stress, growth arrest, DNA damage, and radiotherapy. It exerts tumor-suppressive functions by maintaining genomic stability, inhibiting abnormal proliferation, and promoting the clearance of damaged cells ^[6].

As a typical tumor-suppressive lncRNA, GAS5 primarily functions through several mechanisms.

- (1) It acts as a competing endogenous RNA (ceRNA) to sequester miRNAs and relieve their inhibitory effects on target mRNAs ^[7]
- (2) It directly binds to protein molecules to regulate their subcellular localization and activity.
- (3) It participates in DNA damage repair and cell cycle checkpoint regulation.
- (4) It modulates the expression of apoptosis-related genes to initiate the intrinsic apoptotic pathway.

2.2. Aberrant expression of GAS5 in prostate cancer and its clinical significance

Multiple clinical samples and cellular experiments have confirmed that GAS5 expression is significantly lower in prostate cancer tissues than in adjacent normal tissues. It is even lower in castration-resistant prostate cancer (CRPC) cells, suggesting that its loss is associated with disease progression and enhanced malignant phenotypes ^[8]. Studies in cell lines, including LNCaP, DU145, and PC-3, show that GAS5 expression is markedly reduced compared to normal prostate epithelial cells. There is further downregulation in radioresistant cell lines, indicating that low GAS5 expression is an important molecular feature of

radioresistance in prostate cancer ^[9].

Clinical correlation analyses have demonstrated that low GAS5 expression is significantly associated with higher Gleason scores, advanced TNM stages, lymph node metastasis, and early postoperative recurrence in prostate cancer. It serves as an independent adverse prognostic factor ^[10]. Furthermore, GAS5 expression levels are closely associated with radiotherapy response. There is significantly higher expression in tumor tissues from radiosensitive patients than in those from resistant patients. This suggests that GAS5 may serve as a biomarker for predicting radiotherapy sensitivity in prostate cancer ^[11].

3. Core molecular mechanisms by which GAS5 regulates radiosensitivity in prostate cancer

3.1. Competing endogenous RNA (ceRNA) mechanism

The ceRNA mechanism is a central pathway through which GAS5 regulates radiosensitivity in prostate cancer. GAS5 sequesters specific miRNAs via sequence complementarity. This blocks their degradation or translational inhibition of target mRNAs, thereby restoring the expression of tumor-suppressive genes and reversing radioresistance ^[12].

miR-18a is overexpressed in prostate cancer and promotes proliferation and radioresistance by inhibiting tumor-suppressive genes, including PTEN and BIM ^[13]. GAS5 directly targets and inhibits miR-18a activity, upregulating PTEN expression and suppressing excessive activation of the PI3K/Akt pathway. It also enhances radiotherapy-induced DNA damage and apoptosis. α -Solanine exerts radiosensitizing effects by upregulating the GAS5/miR-18a axis ^[14].

GAS5 also sequesters miR-320a, relieving its inhibitory effect on RAB21. RAB21 inhibits proliferation and migration by regulating cytoskeletal dynamics and membrane trafficking. It also enhances radiotherapy-induced G2/M phase arrest and apoptosis. *In vitro* and *in vivo* experiments have confirmed that this axis significantly improves radiosensitivity in prostate cancer.

Additionally, GAS5 targets miR-103, miR-21, and others. It inhibits cell cycle progression and enhances apoptotic responses by modulating pathways such as AKT/mTOR and MAPK. In this way, it synergistically enhances radiotherapy sensitivity.

3.2. Regulation of DNA damage repair response to enhance radiotherapy-induced genomic damage

Radiotherapy exerts its cytotoxic effects by inducing DNA double-strand breaks (DSBs). Efficient DSB repair is a key mechanism of radioresistance ^[15]. GAS5 enhances radiosensitivity by inhibiting DNA damage repair through two mechanisms. First, it suppresses key DSB repair proteins, such as Rad51 and Ku70/Ku80, thereby inhibiting homologous recombination (HR) and non-homologous end joining (NHEJ). This prolongs the duration of γ -H2AX foci and exacerbates damage accumulation ^[16]. Second, GAS5 regulates DNA damage checkpoints. It activates the ATM/ATR-Chk1/Chk2 pathway, induces G1/S or G2/M phase arrest, and provides a window for failed DNA repair and the initiation of apoptosis. This prevents damaged cells from escaping proliferation.

Reprogramming cell cycle and apoptosis programs is an important pathway through which GAS5 enhances radiosensitivity ^[17]. GAS5 upregulates cyclin-dependent kinase inhibitors, including p21 and p27. It downregulates cyclins such as CyclinD1 and CDK4, thereby inducing G0/G1 or G2/M phase arrest. This

reduces the proportion of S-phase cells, which are more resistant to radiotherapy ^[18]. In regulating apoptosis, GAS5 upregulates pro-apoptotic proteins such as Bax and Cleaved Caspase-3/9. It also downregulates anti-apoptotic proteins such as Bcl-2, thereby activating the mitochondrial apoptotic pathway and lowering the apoptotic threshold ^[19]. Furthermore, GAS5 inhibits epithelial-mesenchymal transition (EMT) by downregulating N-cadherin and Vimentin while upregulating E-cadherin. This reduces invasive and metastatic capabilities and reverses EMT-mediated radioresistance.

Reprogramming of the cell cycle and apoptosis (programmed cell death) pathways is an important mechanism by which GAS5 enhances radiosensitivity ^[17]. GAS5 upregulates cyclin-dependent kinase inhibitors such as p21 and p27 (proteins that block cell division) while downregulating cyclins such as CyclinD1 and CDK4 (proteins that promote cell division), thereby inducing G0/G1 or G2/M phase arrest (points where the cell can pause before duplicating its DNA or dividing) and reducing the proportion of S-phase cells, which are more resistant to radiotherapy ^[18]. In regulating apoptosis, GAS5 upregulates pro-apoptotic proteins such as Bax and Cleaved Caspase-3/9 (which promote cell death) and downregulates anti-apoptotic proteins such as Bcl-2 (which prevent cell death), thereby activating the mitochondrial apoptotic pathway and increasing the likelihood of apoptosis ^[19]. Furthermore, GAS5 inhibits epithelial-mesenchymal transition (EMT, a process where cancer cells gain the ability to move and invade by losing cell adhesion), by downregulating N-cadherin and Vimentin (proteins associated with cell movement) while upregulating E-cadherin (a protein that promotes cell adhesion), reducing invasive and metastatic capabilities, and reversing EMT-mediated radioresistance.

3.3. Regulation of key signaling pathways to synergistically enhance radiosensitivity

GAS5 also achieves synergistic radiosensitization by modulating core tumor signaling pathways. The PI3K/Akt/mTOR pathway is frequently hyperactivated in radioresistant tumors; GAS5 inhibits this pathway by upregulating PTEN via the ceRNA mechanism, reducing cellular proliferation and repair capacity ^[20]. The MAPK/ERK pathway regulates cell proliferation and anti-apoptotic signaling; GAS5 suppresses ERK phosphorylation, blocking pro-survival signals and enhancing radiotherapy-induced apoptosis. The NF-κB pathway is associated with inflammation and treatment resistance; GAS5 inhibits p65 nuclear translocation, reducing the transcription of downstream anti-apoptotic genes and lowering tumor cell radioresistance.

4. Issues and prospects

Significant progress has been made in research on the regulation of radiosensitivity in prostate cancer by GAS5, yet clinical translation still faces numerous challenges. GAS5 is widely expressed in normal tissues and lacks tumor specificity, making tumor-targeted delivery and minimizing impacts on normal tissues critical challenges. The poor in vivo stability and susceptibility to nuclease degradation of lncRNAs necessitate the development of more efficient delivery systems. Prostate cancer exhibits significant molecular heterogeneity, with variations in GAS5 regulatory pathways across subtypes, necessitating clarification of the mechanisms underlying GAS5 regulation in each subtype for precise regulation. Current research is predominantly based on foundational experiments and lacks validation through large-sample, prospective clinical studies of its effectiveness as a biomarker and target.

Future research should focus on four directions: exploring functional differences among GAS5 splice

variants to develop specific radiosensitizing tools; constructing tumor-targeted delivery systems for efficient and controlled release; conducting clinical cohort studies to establish GAS5-based predictive models for radiotherapy sensitivity; and investigating combination strategies involving GAS5 with immunotherapy and PARP inhibitors to establish multimodal treatment systems. With advancements in mechanistic research and technology, GAS5 holds promise as a crucial target for precision radiotherapy in prostate cancer, offering new avenues to improve patient prognosis.

5. Conclusion

LncRNA GAS5 is under expressed in prostate cancer and is closely associated with disease progression, poor prognosis, and radioresistance, serving as a core molecule in regulating radiosensitivity. GAS5 positively enhances radiosensitivity and reverses resistant phenotypes in prostate cancer through multiple mechanisms, including ceRNA networks, inhibition of DNA damage repair, reprogramming of the cell cycle and apoptosis, and regulation of tumor signaling pathways. Radiosensitizing strategies targeting GAS5 have demonstrated favorable effects in in vitro and in vivo experiments, possessing significant clinical translation potential. As research progresses, GAS5 will emerge as a new target for radiosensitization in prostate cancer, facilitating the development of precision radiotherapy and improving patient survival.

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Ultra-minimally Invasive Prostatic Urethral Dilation for Small-volume Benign Prostatic Obstruction: A Case Report

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Abstract: *Background:* Small-volume benign prostatic obstruction (BPO) represents a distinct clinical phenotype in which lower urinary tract symptoms (LUTS) are often driven by functional and microenvironmental factors rather than anatomical enlargement. Conventional treatment strategies may be less effective in this subgroup. *Case presentation:* We report the case of a 66-year-old male with severe LUTS and a small prostate volume (20 mL) who showed inadequate response to medical therapy. The patient underwent prostatic urethral dilation (PUD) using an ultra-minimally invasive prostate dilation catheter (Longevity bar). At 3-month follow-up, improvements were observed in symptom score, urinary flow rate, and post-void residual volume, while sexual function was preserved, and no procedure-related complications occurred. *Conclusion:* PUD may provide a potential treatment option for selected patients with small-volume BPO. Further studies are needed to determine its long-term efficacy and clinical role.

Keywords: Benign prostatic obstruction; Prostatic urethral dilation; LUTS; Minimally invasive therapy

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1. Introduction

Benign prostatic hyperplasia (BPH) is a common pathological basis of lower urinary tract symptoms (LUTS) in aging men ^[1]. Clinically, its significance lies not only in prostate enlargement itself, but also in the development of benign prostatic obstruction (BPO), which reflects increased bladder outlet resistance and impaired urinary emptying ^[2,3]. However, increasing evidence suggests that this volume-based paradigm is insufficient, particularly in patients with small prostate volume, where symptom severity often shows poor correlation with gland size ^[4]. In this context, small-volume BPO represents a clinically meaningful phenotype, because the key problem is not marked glandular enlargement but the presence of outlet

resistance and impaired urinary emptying.

In this subgroup, functional factors including increased smooth muscle tone, chronic inflammation, fibrosis, and neural dysregulation are considered to play a key role in the development of obstruction and symptom generation ^[5–8]. These observations have prompted growing interest in treatment approaches that target underlying functional mechanisms rather than relying solely on tissue removal ^[9].

Prostatic urethral dilation (PUD) is an emerging ultra-minimally invasive technique that reduces urethral resistance through controlled mechanical expansion without tissue ablation ^[10]. By preserving mucosal integrity and limiting structural disruption, PUD may be particularly relevant in patients with predominantly functional obstruction ^[10]. This mechanism is especially relevant to small-volume BPO, where reducing urethral resistance may be more important than reducing prostate volume.

However, clinical evidence regarding the application of PUD in small-volume BPO remains limited, and real-world case-based insights are needed to better define its role in this specific phenotype.

2. Case presentation

A 66-year-old male presented with a 2-year history of progressively worsening lower urinary tract symptoms (LUTS), including urinary frequency, nocturia (1–2 times per night), weak urinary stream, and a sensation of incomplete bladder emptying. These symptoms significantly affected his daily activities and sleep quality.

Baseline evaluation showed an International Prostate Symptom Score (IPSS) of 22 and a quality-of-life (QoL) score of 5. Uroflowmetry demonstrated a maximum urinary flow rate (Qmax) of 15 mL/s, and ultrasound revealed a post-void residual (PVR) volume of 151 mL. Transrectal ultrasonography measured a prostate volume of 20 mL.

The patient had received α_1 -adrenergic receptor antagonist therapy for 6 months, with limited symptom improvement ^[11,12]. Given the small prostate volume and concerns regarding potential sexual dysfunction, the patient declined surgical options such as transurethral resection of the prostate (TURP) and holmium laser enucleation of the prostate (HoLEP) ^[2,13].

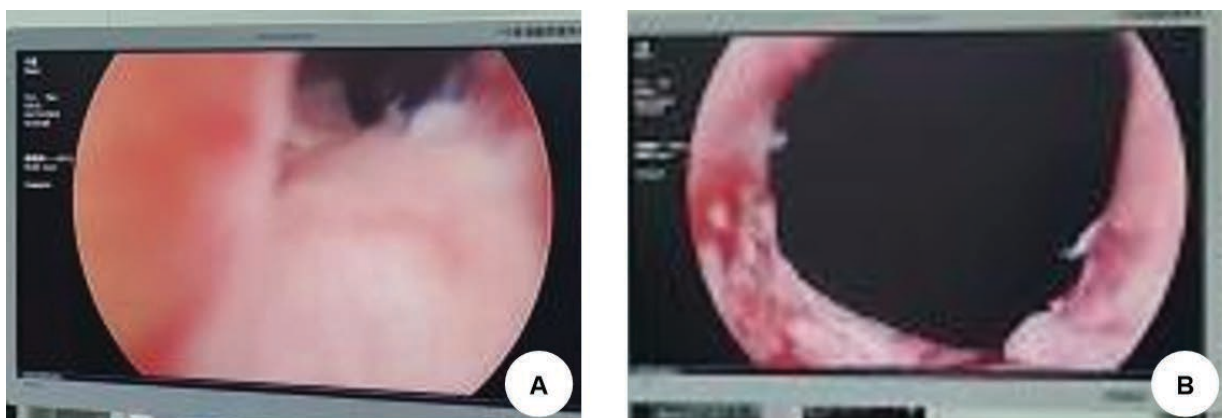
After informed consent, prostatic urethral dilation was performed under general anesthesia. An ultra-minimally invasive prostate dilation catheter (Longevity bar: F16-32T) was inserted transurethrally under cystoscopic guidance. The balloon was gradually inflated to a working pressure of approximately 0.3 MPa and maintained for 10 minutes to achieve dilation of the prostatic urethra. Positioning and expansion were continuously assessed during the procedure.

The total procedure time was approximately 20 minutes. No intraoperative complications occurred, and the Foley catheter was removed within 24 hours.

At the 3-month follow-up, clinical parameters improved. The IPSS decreased from 22 to 15, Qmax increased from 15 to 19 mL/s, and PVR decreased from 151 mL to 30 mL. Sexual function was preserved, with no evidence of retrograde ejaculation or erectile dysfunction.

No adverse events, including urinary incontinence, urinary tract infection, or urethral stricture, were observed during follow-up.

Comparative cystoscopic evaluation demonstrated improved bladder neck opening following PUD and Longevity bar. The previously obstructed segment of the prostatic urethra was dilated, with restoration of luminal patency. No mucosal injury or bleeding was observed, and the dilation contour appeared well defined (**Figure 1**).



A: Preoperative cystoscopic image of the patient; **B:** Postoperative cystoscopic image of the patient.

Figure 1. Comparative cystoscopic images of the patient before and after PUD surgery.

3. Discussion

This case suggests the potential role of PUD in the management of small-volume benign prostatic obstruction (BPO) ^[4]. In contrast to conventional approaches that primarily focus on reducing prostate volume, PUD, and the Longevity bar act by decreasing urethral resistance through controlled mechanical expansion ^[2,3,10,14].

In this patient, the relatively preserved Qmax despite severe LUTS suggests the presence of functional obstruction ^[15]. Factors such as increased urethral tone, reduced urethral compliance, and possible bladder dysfunction may contribute to symptom severity ^[16]. This observation is in line with previous reports indicating that, particularly in small-volume BPO, symptom burden does not always correlate with prostate size, and functional components may play a more prominent role ^[4,17].

The improvements in urinary flow and symptom score observed after the procedure indicate that functional factors were likely predominant in this case. Mechanical dilation may reduce outlet resistance without inducing thermal injury or ischemic necrosis, thereby preserving tissue integrity ^[18]. In addition, by avoiding tissue destruction, this approach may reduce the risk of secondary inflammatory responses and fibrosis, which have been implicated in persistent or recurrent LUTS ^[7,19,20].

Preservation of sexual function was also observed during follow-up ^[21]. This finding is clinically relevant, as ejaculatory dysfunction remains a frequent concern after resective procedures such as TURP or laser-based techniques ^[21]. For patients who prioritize the maintenance of sexual function, non-resective approaches may offer a more acceptable therapeutic option ^[9].

When compared with other minimally invasive therapies, PUD differs in its mechanism of action. Procedures such as prostatic urethral lift (PUL) primarily relieve obstruction through mechanical retraction, while techniques such as Rezūm or prostatic artery embolization (PAE) rely on tissue ablation or ischemia ^[9]. In contrast, PUD and the Longevity bar can directly target the dynamic component of obstruction without altering tissue viability ^[10]. This characteristic may be particularly relevant in patients with small prostate volume, where anatomical enlargement is limited and functional factors are more prominent ^[4].

From a practical perspective, PUD and the Longevity bar may also offer advantages in terms of procedural simplicity and recovery. Under appropriate clinical conditions, this procedure may be performed

under local anesthesia in selected patients, with a relatively short operative time and early catheter removal, which may facilitate recovery and reduce perioperative burden ^[22]. However, these potential benefits require confirmation in larger clinical cohorts.

These observations should be interpreted with caution. Evidence on PUD remains limited, and questions remain regarding its long-term outcomes, durability of symptom relief, and appropriate patient selection. In addition, pressure-flow urodynamic assessment was not performed in this case, which limits further characterization of the underlying mechanism. Further prospective studies are warranted to clarify its role in clinical practice.

This case also highlights an important clinical distinction between prostate size and the mechanism of obstruction. In routine practice, men with a small prostate may be considered less likely to have clinically relevant obstruction because anatomical enlargement is limited. However, gland size alone does not fully explain LUTS severity. Current evidence and guidelines emphasize that the assessment of male LUTS should integrate symptom burden, urinary flow, post-void residual volume, prostate morphology, and the possibility of functional obstruction ^[23]. In selected patients, increased outlet resistance may arise from bladder neck stiffness, periurethral fibrosis, enhanced smooth muscle tone, chronic inflammatory remodeling, or impaired relaxation of the prostatic urethra rather than from glandular enlargement itself ^[7,24]. Therefore, a treatment strategy guided only by prostate volume may overlook the dominant pathophysiological mechanism, particularly in patients with severe symptoms and substantial residual urine despite a small gland ^[4,25].

In the present patient, the prostate volume was 20 mL, yet the symptom burden was severe, and the baseline PVR was markedly elevated. These findings suggest that the obstruction was unlikely to be explained by tissue bulk alone. Reduced urethral compliance and functional narrowing of the prostatic urethra may have contributed substantially to impaired bladder emptying. From this perspective, PUD represents a mechanism-directed intervention rather than a volume-reducing procedure. Instead of removing, vaporizing, or devascularizing prostatic tissue, controlled circumferential dilation aims to enlarge the functional urethral channel and reduce outlet resistance ^[10]. This non-resective principle is particularly relevant for small-volume BPO, where the therapeutic target is often urethral resistance rather than excess adenomatous tissue ^[4,10].

Another point of interest is mucosal preservation. Local tissue injury, edema, inflammation, and fibrotic repair may contribute to persistent or recurrent LUTS after some interventions for BPH/BPO ^[26,27]. A dilation-based approach avoids thermal injury and tissue necrosis, which may help reduce secondary inflammatory remodeling. In this case, postoperative cystoscopy showed improved opening of the bladder neck and prostatic urethra, with no obvious mucosal bleeding or structural disruption. Although this single observation cannot establish long-term benefit, it provides visual support for the concept that controlled dilation can restore luminal patency while maintaining mucosal integrity ^[10].

Appropriate patient selection is essential. Based on the mechanism of action, PUD may be most relevant for patients with small-to-moderate prostate volume, suspected functional obstruction, inadequate response to medical therapy, and a strong preference for preserving sexual function ^[4,9,10]. It may also be considered for elderly or medically vulnerable patients in whom a shorter, less invasive procedure is desirable, although this indication requires further validation. Preoperative evaluation should therefore extend beyond prostate volume and include IPSS, QoL score, uroflowmetry, PVR, prostate imaging, cystoscopic assessment, and, when clinically indicated, urodynamic testing. Patients with severe detrusor underactivity, neurogenic bladder, active urinary infection, urethral stricture, or suspected malignancy should be carefully evaluated

before considering this approach ^[28].

The reduction in PVR observed in this case is also noteworthy. Although the increase in Q_{max} was moderate, the decrease in residual urine from 151 mL to 30 mL suggests a meaningful improvement in bladder emptying efficiency. PVR reflects the interaction between outlet resistance and detrusor function, and therefore provides complementary information to Q_{max} alone ^[29]. This is particularly relevant in small-volume BPO, where baseline urinary flow may not always be severely reduced despite bothersome symptoms, incomplete emptying, and impaired quality of life. In such patients, treatment response should be interpreted using both subjective symptom scores and objective functional indicators ^[4].

Several limitations should be acknowledged. This is a single case with short-term follow-up, and urodynamic testing was not performed; therefore, the underlying obstruction mechanism cannot be definitively confirmed. The durability of symptom relief after PUD also remains uncertain. Future prospective studies should use standardized selection criteria, longer follow-up, validated symptom and functional outcomes, and serial cystoscopic or imaging evaluation where appropriate. Comparative studies against medical therapy, TURP, HoLEP, PUL, Rezūm, prostatic artery embolization, and other minimally invasive treatments would be valuable. Such evidence is needed to determine whether PUD has a defined role in the treatment pathway for small-volume BPO and whether its non-resective, mucosa-preserving mechanism can translate into durable improvement with fewer functional complications.

4. Limitations

This report has several limitations. First, it represents a single case with a relatively short follow-up period. Second, a pressure-flow urodynamic assessment was not performed to characterize the underlying mechanism of obstruction further. Therefore, the generalizability of these findings remains limited.

5. Conclusion

This case suggests that prostatic urethral dilation may provide significant symptomatic and functional improvement in patients with small-volume BPO while preserving sexual function. As a non-resective and mechanism-based approach, PUD may represent a potential addition to the current therapeutic options. A phenotype-driven approach based on underlying mechanisms may allow more individualized management of patients with LUTS ^[30]. Further prospective studies with larger sample sizes and longer follow-up are warranted to confirm these findings and clarify their clinical role. Ethics approval and consent to participate: This study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board waived ethical approval, as this is a single case report and does not involve identifiable patient information. Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal upon request.

Disclosure statement

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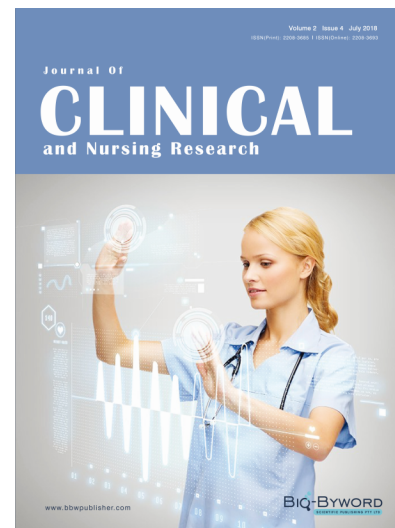
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