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*Original Article*

# Follow-up and histocompatibility observation of urethral reconstruction with different materials

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**Abstract:** Objective: Our objective is to observe the long-term surgical results of urethral reconstruction using either pedicled penile flaps or lingual mucosa grafts. We also assess the histocompatibility of the reconstructed urethra. Materials and Methods: Clinical data of patients with anterior urethral stenosis undergoing urethra reconstruction by applying different materials were collected from 2014 to 2022 in the Second Hospital of Hebei Medical University. We assessed their efficacy and the occurrence of complications. Patients who required reoperation due to complications were selected. Sections of the reconstructed urethra created with various materials were excised during repair procedures. The excised tissues underwent hematoxylin-eosin staining and immunohistochemistry. Comparison with the original histological morphology was conducted to evaluate histocompatibility. Results: 42 of the 55 patients were cured which showed a surgical success rate of 76.36%. The success rate of urethra reconstruction surgery utilizing lingual mucosa is 71.43% and that of surgeries using pedicled penis flaps is 79.41%. The long-term prognosis of the two groups is similar ($P > 0.05$). Observations show that the histological morphology of the original epithelium gradually disappeared, leading to adaptive changes to the urinary environment with favorable histocompatibility. Conclusion: The application of lingual mucosal and pedicled penis flaps for urethral reconstruction both have a high surgical success rate. The long-term follow-up results are positive. Both methods are viable for urethral reconstruction and exhibit favorable histocompatibility.

**Keywords:** Anterior urethral stricture, pedicled penis flaps, lingual mucosa, tissue compatibility

## Introduction

Urethral stricture is a prevalent condition in the field of urology. The latest statistical data indicate an annual incidence rate of urethral stricture of approximately 0.6%, with an increasing trend [1]. It is defined as a pathological condition marked by the presence of an abnormally narrow lumen or the contraction of the external urethral sphincter along any segment of the urethra, leading to elevated urethral resistance. The disparity in diameter between a urethral stricture and a healthy urethra is contingent upon the precise location and severity of the stricture. Conservative management of urethral stricture often proves insufficient in achieving satisfactory outcomes, necessitating surgical intervention for most patients. Surgical interventions have advanced significantly, encompassing diverse approaches, including urethral dilation, urethral stricture incision, urethral end-to-end anastomosis, and graft replacement urethroplasty [2]. Often, alternative materials are required to replace the urethra in patients with longer narrow segments, aiming to minimize urethral tension [3]. Commonly employed urethral substitute materials include lingual mucosa and pedicled penis flaps. Related animal experiments demonstrate the favorable tissue adaptability and extensive clinical applicability of both materials [4, 5]. Nevertheless, there is a scarcity of studies involving human subjects. This study aims to conduct a long-term follow-up of patients undergoing urethral reconstruction using different materials at our hospital, aiming to compare the long-term effects following urethral repair. Based on the findings, we conduct a comprehensive analysis to determine which material exhibits a superior long-term therapeutic effect. Simultaneously, we also investigate the histological changes following urethral reconstruc-

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tion. Additionally, we analyze histocompatibility and explore the association between histocompatibility and postoperative complications, aiming to provide theoretical support for the selection of substitute materials in clinical practice.

*General information*

Patients with urethral stricture were predominantly diagnosed at the Second Hospital of Hebei Medical University between January 2014 and December 2022. All patients met the indications for surgical intervention of urethral stricture and underwent urethral reconstruction using either lingual mucosa grafts or pedicled penile flaps. Subsequently, we collected the clinical data of these patients and conducted follow-ups on the surgical outcomes. Reconstruction of specific urethral segments may be necessary during repairs if postoperative complications necessitate subsequent intervention in patients undergoing urethral reconstruction with various materials. All specimens in this study were obtained from inpatients in the Department of Urology at our hospital. Informed consent was obtained from all patients before surgery and the study protocol was approved by the ethics committee.

*Inclusion criteria, exclusion criteria and indications for surgery*

Inclusion criteria: (1) urethral stricture initial diagnosis per the guidelines for diagnosis and treatment of urological and andrological diseases; (2) no comorbid diagnoses interfering with the treatment outcome and surgical procedures; (3) surgical indications for urethroplasty using diverse materials as implemented in our institution; (4) removal of urethral catheterization as per physician directive with subsequent successful urination through the urethra; (5) availability of complete patient data and capability of patients to comply with follow-up assessments.

Exclusion criteria: (1) individuals failing to meet the criteria for initial diagnosis; (2) patients not undergoing urethral reconstruction with different materials; (3) those using multiple materials for urethral reconstruction concurrently; (4) those affected by incomplete data or concurrent diseases; (5) inability to urinate spontaneously postoperatively for various reasons; (6) patients requiring prioritization for the treatment of comorbid conditions; (7) patients lost to follow-up or unable to comply with it; (8) individuals not satisfying the inclusion criteria.

Indications for surgery: (1) a urethral stricture resulting in severe dysuria or urinary retention represents the primary indication for surgical intervention. (2) urethral stricture causing impediments in urinary flow, manifesting as difficulty in urination or urinary retention. These conditions may lead to severe complications such as urinary tract infections, urolithiasis, and renal insufficiency, any of which can significantly impact the patient's quality of life. (3) determine the presence and extent of urethral stricture through objective examinations, such as uroflow rate measurement, urethrography, etc. Surgery is also indicated when there is a definite stricture, low urine flow rate, straining to urinate and symptoms of voiding.

## Method

*Methods of reconstructing the urethra with lingual mucosa*

Patients are positioned in the lithotomy stance after nasal catheterization. The site of urethral stenosis is ascertained through preoperative urethrography. Subcutaneous tissues are incised layer by layer through the penis, scrotum, or perineum to expose the corpus cavernosum of the urethra. After dissecting the aforementioned tissue, the stenotic site was adequately exposed. For oral mucosa incision, the lower lip is retracted to expose its mucosa. A solution of normal saline infused with epinephrine (1 mg/mL epinephrine mixed with normal saline at a volume ratio of 1:100) is administered into the submucosa. Dissection proceeds through the submucosal layer to harvest the mucosal tissue. Subsequently, the harvested mucosal tissue is trimmed and placed in normal saline for later use. The lingual mucosal graft is sutured using 5-0 absorbable sutures. The dorsal wall of the constricted urethral segment is incised, and all scar tissue is excised until the tunica albuginea of the corpus cavernosum is revealed. The oral mucosal graft is meticulously released on both sides to allow even distribution over the surface of the tunica albuginea. Anastomosis of the oral mucosal graft with the native urethral mucosa is carried out using 6-0 absorbable sutures to reestablish the integrity of the urethral plate. The ure-

thra is then sutured enclosing an indwelling support tube (a 14-18 F catheter, chosen based on the urethral circumference). Postoperatively, the penis is wrapped with an elastic bandage and the scrotal incisions are dressed under suitable pressure for three days.

*Methods of reconstructing the urethra with pedicled penis flaps*

After successful anesthesia, the patient is placed in a supine position. The location of urethral stenosis is ascertained based on preoperative urethrography, and a longitudinal incision is created at the corresponding site. The subcutaneous tissue is incised layer by layer to expose the urethra. The ventral cavernous body of the urethra in the narrowed segment is incised longitudinally, and the urethral scar tissue is excised. The foreskin is excised from the ventral cavernosa membrane of the penis. Finally, a support tube is placed (a 14 to 18 French catheter, chosen based on urethral circumference), and the flap is rotated to cover the urethral defect. The flap is anastomosed to the urethral mucosa using 5-0 absorbable sutures. A portion of the cavernosa membrane tissue is isolated to cover the urethral anastomosis, thus preventing infiltration leaking. The subsequent postoperative management aligns with that of the lingual mucosal graft urethroplasty.

*Follow-up method*

The relevant patient data, including basic information, diagnosis, location, and length of the urethral stricture, as well as the course of the disease and the mode of operation, are gathered systematically. Follow-up assessments typically occur at 3, 6, 12, and 24 months postoperatively, with subsequent on-demand follow-ups tailored to the patient's specific needs. The clinical data, including operative outcomes and postoperative complications, are obtained via telephone follow-ups and hospital revisits. Follow-up protocols encompassed, but were not limited to, assessing (1) Current urinary function and any improvement in postoperative dysuria relative to the preoperative state. (2) The presence of conditions such as urethral stricture, urethral fistula, or urethral diverticulum and any associated complications. (3) Any additional discomforts including speech disturbances and changes in taste following lingual mucosal removal. Should abnormalities be detected, timely and appropriate therapeutic interventions will be employed to mitigate complications. Furthermore, patients are advised to hydrate adequately, urinate frequently, and maintain perineal hygiene postoperatively to prevent secondary infections. If symptoms such as decreased urine stream, prolonged urination times, or hesitancy are noted, prompt medical consultation should be sought for further evaluation and treatment.

*Hematoxylin-eosin staining and observation method*

Required reagents: Eosin dye, hematoxylin stain, xylene, gradient ethanol, distilled water, hydrochloric acid alcohol, and neutral gum.

Staining method: Formaldehyde-fixed tissues were cut in an appropriate amount. Then they were dehydrated and dewaxed using gradient ethanol and xylene solutions. The tissues were made into slices by using wax. Staining was performed using hematoxylin and eosin after treatment with xylene and gradient ethanol. We used neutral glue to seal the slices. Lastly, we observed the slices under a camera microscope.

Observation methods: The histomorphology of various materials before and after urethral reconstruction is observed using electron microscopy. We record and compare the mucosal layer and the extent of infiltration by inflammatory cells to analyze compatibility.

*Immunohistochemistry (IHC) staining and observation method*

Required reagents: Alpha smooth muscle Actin Protein (α-SMA) antibody (Abcam, ab-7753), cytokeratin (CK) antibody (Proteintech, 55135-1-AP), hematoxylin stain, citrate buffer, PBS buffer, immunohistochemical kit (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., batch number 2210B1008), antibody enhancer, 3% hydrogen peroxide, serum sealant, DAB chromogenic solution, xylene, gradient ethanol, distilled water, hydrochloric acid alcohol, neutral gum.

Staining method: Pathological slices were prepared using gradient ethanol and xylene solutions. Subsequently, they were rinsed with PBS

**Table 1.** Basic information of patients

| Group | Number of people | Median age (years) | Median course of disease (years) | Mean narrow length (cm) |
|---|---|---|---|---|
| Lingual mucosa group | 21 | 49 (41, 60) | 18 (3, 40) | 8 (6, 12) |
| Pedicled penis flap group | 34 | 17 (2, 39) | 1 (0.8, 4) | 2.5 (1.5, 4.5) |
| *P* | | < 0.0001 | < 0.0001 | < 0.0001 |

**Table 2.** Long-term follow-up of patients

| Group | Totality | Successful | Lose | Success rate |
|---|---|---|---|---|
| Lingual mucosa group | 21 | 15 | 6 | 71.43% |
| Pedicled penis flap group | 34 | 27 | 7 | 79.41% |
| Totality | 55 | 42 | 13 | 76.36% |
| | | | | *P*=0.503 |

buffer solution. We added citric acid solution dropwise and used high-pressure antigen to repair. The tissues were circled using an immunohistochemical pen after cooling to room temperature. Then, they were incubated at 37 degrees with a 3% hydrogen peroxide solution. The first antibody was added dropwise and left for 30 minutes at 37 degrees. Afterward, the slices were placed in a refrigerator at 4 degrees overnight. The next day, horseradish peroxidase-labeled secondary antibody was added when the slices were retrieved. DAB staining solution was added after waiting for half an hour at 37 degrees. The degree of coloration was controlled under the microscope to stop the color reaction promptly. Rapid differentiation was achieved using hydrochloric acid alcohol following hematoxylin staining. The slices were treated with gradient ethanol and xylene solution and sealed with neutral glue. Finally, they were observed and photographed under the microscope.

Methods: Histomorphological analysis was performed on the urethra before and after reconstruction with various materials using an electron microscope. Subsequently, we recorded mucosal integrity as well as the distribution of CK and α-SMA. We categorized the levels of biomarker expression on a spectrum from strong to weak, including strong positive, positive, weak positive, and negative.

*Statistical methods*

The collected data were analyzed and sorted using SPSS26.0 statistical software for statistical analysis. Data following a normal distribution are presented as the mean ± standard deviation, while data following a skewed distribution are presented using the median and interquartile range. The H test was used for comparing all the basic data. A significance level of $P < 0.05$ was applied to determine statistical significance.

## Results

*Follow-up of the long-term efficacy of reconstructing urethra by applying different materials*

A total of 83 patients who applied different materials to reconstruct their urethra were recorded. 28 patients met the exclusion criteria due to the loss of visit, incomplete information, and the simultaneous application of multiple materials for urethral reconstruction, among other reasons. Ultimately, 55 patients met the inclusion criteria and were enrolled in the study. All 55 patients were male, with an average age at the time of surgery of 33.67 ± 22.69 years. The median follow-up period was 48 months (ranging from 3 to 108 months). Age ($P < 0.05$), disease duration ($P < 0.05$), and stenotic segment length ($P < 0.05$) were found to be statistically significant between the banded flap and lingual mucosa groups (**Table 1**). In the lingual mucosa group, which comprised 21 cases, 15 resulted in a cure, and all patients experienced a significant improvement in urination post-surgery. Complications occurred in 6 cases. 4 cases presented with recurrent urethral stenosis. One of them was managed conservatively and three of them were treated with regular urethral dilatation. All patients were able to urinate postoperatively. 2 cases developed urethral fistulae, which were surgically treated and successfully repaired (**Table 2**).

In the pedicled penis flap group of 34 cases, 27 resulted in a cure, and all demonstrated significant improvements in urination post-surgery.

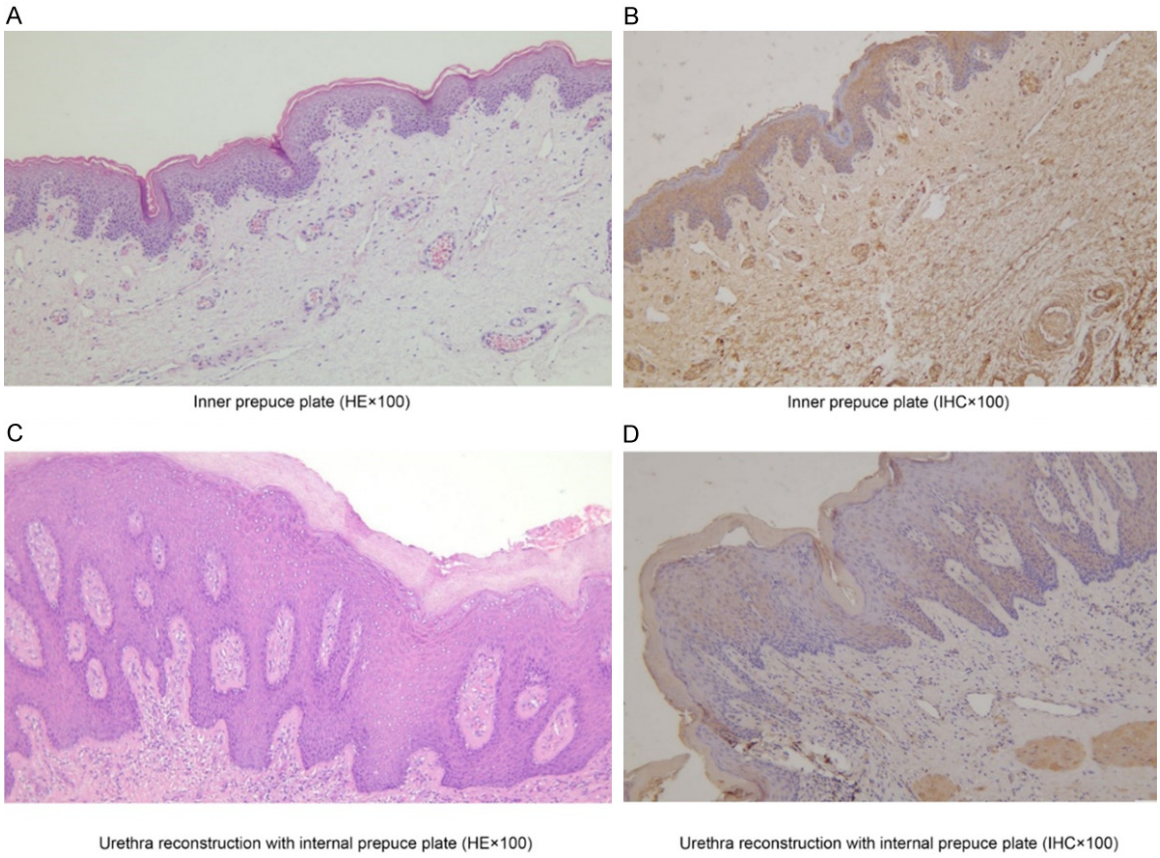


**Figure 1.** Urethra reconstruction with ipedicled penis flaps. A: Inner prepuce plate (HE×100); B: Inner prepuce plate (IHC×100); C: Urethra reconstruction with internal prepuce plate (HE×100); D: Urethra reconstruction with internal prepuce plate (IHC×100). HE staining of the inner plate of the foreskin reveals a division of the mucosa into distinct mucosal and submucosal layers. The evaluation of HE staining conducted 30 years after urethral reconstruction following circumcision demonstrates the division of the reconstructed mucosa into superficial, mucosal, and submucosal layers.

Complications were noted in 7 cases. 4 cases presented with recurrent urethral stricture. One of them received conservative treatment, one of them underwent regular urethral dilatation and two of them required surgical intervention. The urinary function of all patients improved. 3 cases developed urethral fistulae and underwent surgical repair, all of which were successful (**Table 2**).

No statistically significant difference in surgical efficacy was observed between the pedicled penis flap group and the lingual mucosa group ($P > 0.05$), suggesting that different repair materials do not correlate with long-term surgical outcomes (**Table 2**).

*Histocompatibility observation*

A microscopic digital imaging system, comprising a camera microscope and LASX software, is utilized to capture images. Images are captured with an eyepiece and an objective lens, both at 10× magnification. Observation of hematoxylin-eosin and immunohistochemical staining of the pedicled penile flap demonstrates keratinization of the mucosal layer, potentially offering significant protection. The submucosal layer exhibits a rich vascular network. This vascularity renders it suitable for urethral reconstruction (**Figure 1A** and **1B**). Post-reconstruction observations via hematoxylin-eosin and immunohistochemical staining revealed morphological changes in the pedicled penile flap, characterized by superficial structural changes, marked mucosal thickening with multilocular vesicles, and considerable infiltration of anti-inflammatory cells (**Figure 1C** and **1D**). Comparative morphological analysis of the flap before and after urethral reconstruction reveals a gradual loss of the original epithelial architecture. Following urethral reconstruction, the flap

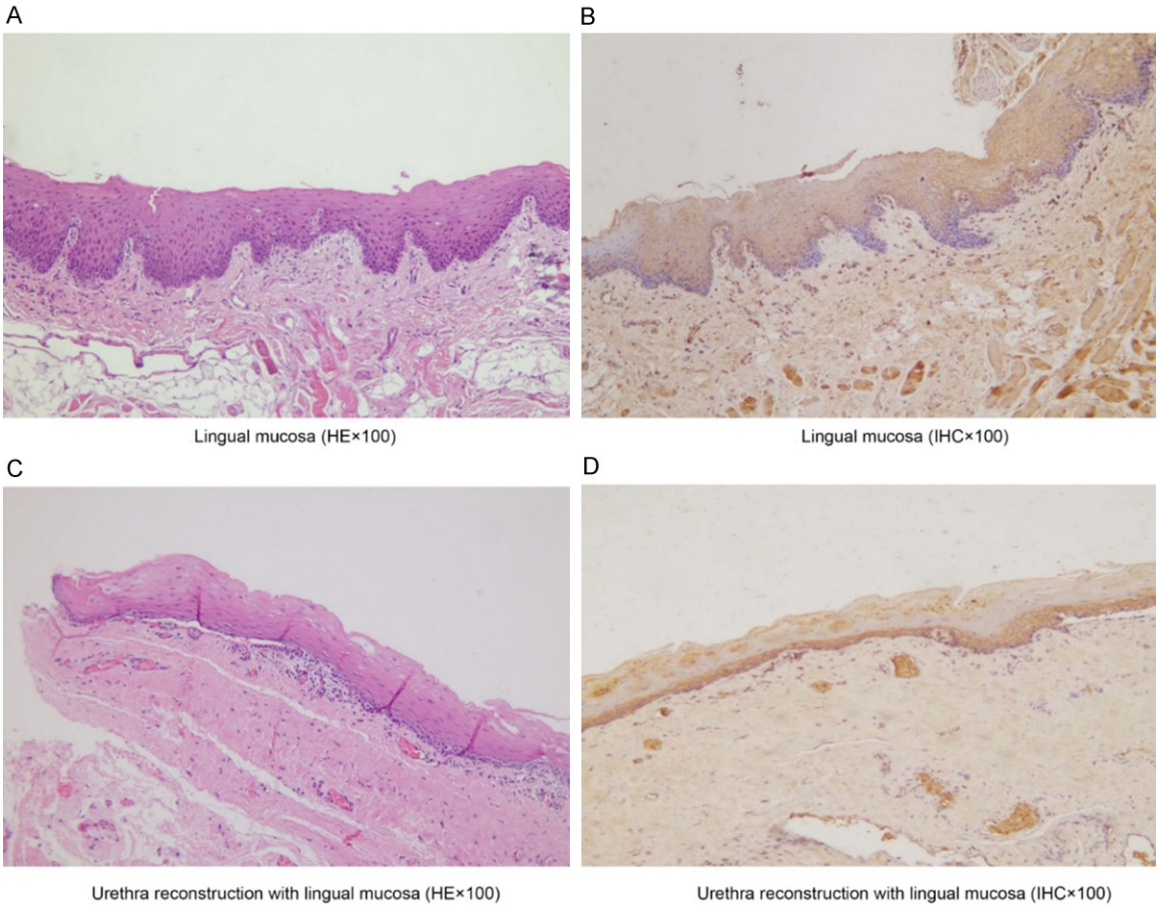


**Figure 2.** Urethra reconstruction with lingual mucosa. A: Lingual mucosa (HE×100); B: Lingual mucosa (IHC×100); C: Urethra reconstruction with lingual mucosa (HE×100); D: Urethra reconstruction with lingual mucosa (IHC×100). HE staining of the inner plate of the foreskin reveals a division of the mucosa into distinct mucosal and submucosal layers. The evaluation of HE staining conducted 30 years after urethral reconstruction following circumcision demonstrates the division of the reconstructed mucosa into superficial, mucosal, and submucosal layers.

demonstrates adaptive alterations, culminating in restored histological integrity and enhanced histocompatibility (**Figure 1A** and **1C**). Long-term observation (30 years post-reconstruction) of immunohistochemical staining indicates that the brown-yellow α-SMA staining in the urethral submucosa signifies potential complication-related muscular fiber deposition (**Figure 1D**).

Observations of hematoxylin-eosin and immunohistochemistry staining of the lingual mucosa indicate that the mucosal layer is rich in keratinization, which provides good resistance to invasion. The interstitium of the submucosal layer is sparse and richly vascularized, which makes it suitable for urethral reconstruction (**Figure 2A** and **2B**). Observations of hematoxylin-eosin and immunohistochemistry staining of the lingual mucosa after reconstruction reveal that the lingual mucosa undergoes histological changes, with thinning of the keratinized mucosal layer and infiltration of inflammatory cells between the mucosal and submucosal layers (**Figure 2C** and **2D**). A comparison of the morphological manifestations of the lingual mucosa before and after the reconstruction of the urethra shows that the original epithelial morphology gradually disappears. Post-reconstruction, the urethra exhibits adaptive changes to the new environment, resulting in new histological stability and favorable histocompatibility (**Figure 2A** and **2B**). Immunohistochemistry staining, 4 years post-urethral reconstruction, indicates that keratin IHC in the mucosa appears brownish-yellow, and the keratinized layer is thinner compared to the original mucosa (**Figure 2D**).

These observations suggest that the original tissue morphology of the lingual mucosa and the pedicled penis flap gradually deteriorates after urethral reconstruction, exhibiting adaptive changes to the new urinary tract environment. Both exhibit favorable histocompatibility. The cause of complications after urethral reconstruction is not related to histocompatibility but may instead be associated with increased α-SMA expression and changes in CK.

## Discussion

Urethral stricture frequently results in urination difficulties and adversely impacts patients' mental health and social function. Patients presenting with urethral stricture typically exhibit urination difficulties and a decreased urinary stream. Beyond subjective symptoms, objective diagnostic data are available. In normal individuals, a urine flow rate exceeding 15 ml/s is considered normal, while a rate of 10-15 ml/s indicates mild obstruction. A flow rate below 10 ml/s indicates significant obstruction. Stenosis can be diagnosed via urethrography. Surgical treatment may be indicated when symptoms of dysuria are present, accompanied by objective diagnostic evidence. As medical technology advances, treatment modalities have become increasingly diversified. However, the effectiveness of therapy is influenced by a range of objective factors, leading to significant variability in cure rates and long-term therapeutic outcomes. In this study, we examine the long-term therapeutic outcomes and histological alterations post-urethral reconstruction, drawing on data from clinical follow-ups and laboratory investigations.

Abundant alternative materials are available for urethral reconstruction. However, the selection of alternative materials is constrained by the patient's preferences, etiology, required graft length, and ease of harvest. Currently, the most prevalent and technologically advanced urethral replacement materials are lingual mucosa and pedicled penile flaps [6-8]. Urethral substitution reconstruction has become a widespread practice in clinical settings. Nonetheless, the reconstructed urethra is susceptible to complications such as urethral restenosis and urethral fistula, which can lead to therapeutic failure, diminishing patient well-being and satisfaction. The optimal material for urethral reconstruction to ensure the best long-term therapeutic outcome remains a focal point of extensive research. Numerous research institutions both domestically and internationally have conducted related studies and compiled statistics. Barbagli et al. [9] conducted a retrospective analysis of 95 patients suffering from bulbous urethral stenosis: urethral reconstruction using penile skin in 45 patients achieved a success rate of 73%, whereas the same procedure employing lingual mucosa in 50 patients had an 84% success rate. Mehrsai et al. [10] conducted a follow-up on 34 patients who underwent urethral reconstruction using lingual mucosa, demonstrating a surgical success rate exceeding 75%. Over 9 years, Fu Q et al. [11] compared the effectiveness and efficacy of sublingual mucosal urethroplasty to pedicled penile flap urethroplasty in treating urethral strictures, finding similar success rates exceeding 80% for both methods, as evidenced by 199 out of 293 patients undergoing pedicled penile flaps and 94 receiving sublingual mucosal grafts. When the success rates of our institution's surgeries are compared to those of other medical facilities, they show comparable outcomes. Additionally, the findings indicate that both procedures have a success rate of over 80%, with comparable outcomes. The aforementioned studies have established that both lingual mucosa and pedicled penile flaps constitute effective materials for urethral reconstruction. Both materials exhibit high and comparable success rates. These materials are widely utilized in clinical practice and yield sustained therapeutic outcomes.

During our follow-up, we identified the following three main points. Firstly, the success rates of urethral reconstructions with various materials are consistently high. The success rates of urethral reconstructions utilizing lingual mucosa and pedicled penile flaps exceed 70%, indicating these are well-established surgical techniques with a significant therapeutic effect worthy of broader clinical adoption. Secondly, the utilization of pedicled penile flaps demonstrates a higher surgical success rate and a better prognosis than that associated with lingual mucosa. Patients undergoing pedicled penile flap procedures tend to be younger, with shorter durations of disease and less extensive stenosis segments, allowing for urethral reconstruction without the need for extensive seg-

mental repair material, resulting in relatively minor surgical trauma and subsequently facilitating postoperative management. Consequently, pedicled penile flaps represent the optimal choice of repair material. Individuals treated with lingual mucosa typically are of an older demographic, present with a more protracted disease history, and have more extensive stenosis segments. The etiology of urethral stenosis is complex and often difficult to define, and some of the patients have a history of circumcision or have a mossy appearance. They increase the difficulty of the surgery, necessitating a relatively long mucosal graft, and entail a longer duration and higher quality of postoperative care for recovery. Consequently, the results indicate that the pedicled penis flap group exhibits a higher surgical success rate and a better prognosis than the lingual mucosa group. Additionally, patients exhibiting postoperative urethral restenosis and urethral fistula are more inclined to pursue elective surgical treatment utilizing alternative approaches if they meet the indications for such procedures. Meanwhile, patients with mild cases are subject to regular review or receive urethral dilation treatment. Individuals acknowledging that their urinary difficulties have not improved substantially, yet lacking in confidence and patience for further alternative treatments, often opt for conservative measures after consultation, such as a long-term indwelling catheter or vesicostomy tube.

The histocompatibility of biological materials is a crucial factor in their evaluation, as it pertains to their interaction with the living environment and the eventual achievement of mutual integration [12]. The selected mucosa for urethral replacement should be non-immunogenic and highly adaptable. Staining observations confirmed that both lingual mucosa and pedicled penis flaps exhibit strong histologic compatibility and can successfully endure in the reconstructed urethral environment without requiring removal. These materials demonstrate the disappearance of their original morphology and exhibit adaptive changes in response to the new environment. Based on our observations, we can confirm the excellent histologic compatibility of both lingual mucosa and pedicled penis flaps.

The normal urethral mucosal epithelial cells exhibit uniform size and tight arrangement with polarization. Various staining methods can be employed to observe the urethral mucosa. Hematoxylin-eosin staining is frequently utilized for histological observation in clinical practice. Hematoxylin-eosin staining allows for the observation of various information, such as tissue structure and mucous membrane morphology. Immunohistochemistry, based on hematoxylin-eosin staining, aids in disease diagnosis and treatment by analyzing the distribution and expression of specific proteins or cytokines. Its guidance facilitates disease diagnosis and treatment. Markers are frequently expressed in the urethral mucosa. α-SMA, a signature protein of smooth muscle cells present in multiple tissues, is regulated by hormones and cell reproduction. It plays a role in tissue repair and fibrosis [13]. CK functions primarily as a protein in keratinocytes, and recent studies indicate that its expression changes in response to the environment [14]. This study involved analyzing the morphology of pedicled penis flaps and the original lingual mucosal tissue, revealing the presence of a keratinized layer that offers effective protection and anti-invasive properties. The submucosa, abundant in blood vessels, facilitates favorable conditions for blood supply restoration post-reconstruction. Both materials serve as excellent reconstruction materials for the urethra. Examination of the histological morphology of the two reconstructed urethras reveals a gradual disappearance of the original mucosal morphology, leading to the emergence of a new histological adaptation performance. This finding indicates the presence of good histocompatibility in both materials. Furthermore, our hypothesis suggests that postoperative complications may be linked to increased α-SMA expression and changes in CK rather than poor histocompatibility. CK is widely expressed in different epithelial cells and serves as the main component.

The technical difficulty of repairing complex urethral strictures arises due to the extent of the urethra that necessitates repair. Complications such as restenosis and the formation of urethral fistulae may arise within the reconstructed urethra. Consequently, the development of tissue engineering materials that can be customized without engendering complications is promising. Reconstructing the urethra with tissue-engineered materials necessitates the preliminary extraction of cells from the

human body. Subsequently, a substantial quantity of replicated cells is cultivated *in vitro*, utilizing absorbable biocompatible materials as scaffolds to ultimately fabricate a urethral substitute. Ultimately, this urethral substitute can be implanted into the human body to establish a functioning urethra [15]. Tissue-engineered materials are non-immunogenic and biodegradable, demonstrating their development relies on histocompatibility. The feasibility of tissue-engineered materials for urethral repair has been validated in animal models; specifically, a study in Germany involved eight Gottingen minipigs whose bladder-urinary epithelial cells were harvested and seeded onto ultrathin collagen. These cells are then cultured in vitro and prepared for use in urethral repair and reconstruction surgeries. Studies have demonstrated that the tested material exhibits complete degradation within 24 weeks postoperatively. Labeling techniques indicate that fluorescence can still be observed at 24 weeks postoperatively, having integrated with the surrounding normal urothelium [16]. To further substantiate the feasibility of utilizing tissue engineering materials in urethral repair, various countries have implemented their use in humans and undertaken extensive long-term follow-up studies. The research group conducted tissue-engineered urethral reconstruction in five male subjects with urethral defects and performed regular follow-up assessments postoperatively. The results indicate that the reconstructed urethras remained functional and were used normally for over six years [17]. Another case study further demonstrates the feasibility [18]. With the advent of 3D printing technology, the selection of materials for urethral repair has become increasingly diverse and developed. Studies have confirmed the feasibility of 3D printing technology [19]. Furthermore, experimental studies have verified the efficacy of composite diaphragms and various biomimetic designs using silk protein materials for urethral reconstruction, thus propelling advancements in the field of synthetic urethral development [20-22]. Ideal synthetic materials for urethral reconstruction should not only simulate normal urethral tissue post-reconstruction but also exhibit minimal rejection risks. Consequently, the study of histocompatibility has attained greater significance. This paper conducts an in-depth analysis from the perspective of histocompatibility to lay a theoretical foundation for the research and development of tissue-engineered urethras.

The choice of materials for the surgical repair of complex urethral strictures in men has consistently presented challenges to clinicians because of the high rate of complications and the poor outcomes following multiple surgeries. This often results in a loss of patient confidence in the treatment. The limitation of this study is that the causes of urethral reconstruction failure were not thoroughly investigated. Future studies are anticipated to further explore this issue. Recent advancements in systematic and in-depth research have significantly accelerated innovation in the treatment of urethral stenosis, particularly through the rapid developments in regenerative medicine and tissue engineering materials. Consequently, there is optimism that future interventions for urethral stenosis will employ superior alternative materials and achieve greater patient satisfaction.

The surgical success rate for urethral reconstruction employing both lingual mucosa and pedicled penis flaps is considerable. The long-term follow-up results have been favorable. Both lingual mucosa and pedicled penis flaps are viable for urethral reconstruction and exhibit favorable histocompatibility.

## Disclosure of conflict of interest

None.

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## References

[1] Zheng X, Han X, Cao D, Xu H, Yang L, Ai J and Wei Q. Comparison between cold knife and laser urethrotomy for urethral stricture: a systematic review and meta-analysis of comparative trials. World J Urol 2019; 37: 2785-2793.

[2] Mangir N and Chapple C. Recent advances in treatment of urethral stricture disease in men. F1000Res 2020; 9: F1000 Faculty Rev-330.

[3] Cheng L, Li S, Wang Z, Huang B and Lin J. A brief review on anterior urethral strictures. Asian J Urol 2018; 5: 88-93.

[4] Song LJ, Xu YM, Hu XY and Zhang HZ. Urethral substitution using autologous lingual mucosal grafts: an experimental study. BJU Int 2008; 101: 739-743.
[5] Fu Q, Deng CL, Song XF and Xu YM. Long-term study of male rabbit urethral mucosa reconstruction using epidermal cell. Asian J Androl 2008; 10: 719-722.
[6] Hmida W, Othmen MB, Bako A, Jaidane M and Mosbah F. Penile skin flap: a versatile substitute for anterior urethral stricture. Int Braz J Urol 2019; 45: 1057-1063.
[7] Wang Z, Zeng X, Chen R, Wang T, Hu J, Wang S and Liu J. Free bladder mucosa graft harvested by water-jet: a novel, minimally invasive technique for urethral reconstruction. Exp Ther Med 2018; 16: 2251-2256.
[8] Granieri MA, Zhao LC, Breyer BN, Voelzke BB, Baradaran N, Grucela AL, Marcello P and Vanni AJ. Multi-institutional outcomes of minimally invasive harvest of rectal mucosa graft for anterior urethral reconstruction. J Urol 2019; 201: 1164-1170.
[9] Barbagli G, Balò S, Montorsi F, Sansalone S and Lazzeri M. History and evolution of the use of oral mucosa for urethral reconstruction. Asian J Urol 2017; 4: 96-101.
[10] Mehrsai A, Djaladat H, Salem S, Jahangiri R and Pourmand G. Outcome of buccal mucosal graft urethroplasty for long and repeated stricture repair. Urology 2007; 69: 17-21; discussion 21.
[11] Fu Q, Zhang Y, Zhang J, Xie H, Sa YL and Jin S. Substitution urethroplasty for anterior urethral stricture repair: comparison between lingual mucosa graft and pedicled skin flap. Scand J Urol 2017; 51: 479-483.
[12] Xue JD, Gao J, Fu Q, Feng C and Xie H. Seeding cell approach for tissue-engineered urethral reconstruction in animal study: a systematic review and meta-analysis. Exp Biol Med (Maywood) 2016; 241: 1416-1428.
[13] Sa Y, Li C, Li H and Guo H. TIMP-1 induces α-smooth muscle actin in fibroblasts to promote urethral scar formation. Cell Physiol Biochem 2015; 35: 2233-2243.
[14] Souza GF, Calado AA, Delcelo R, Ortiz V and Macedo A Jr. Histopathological evaluation of urethroplasty with dorsal buccal mucosa: an experimental study in rabbits. Int Braz J Urol 2008; 34: 345-351; discussion 351-354.
[15] Chapple C. Tissue engineering of the urethra: where are we in 2019? World J Urol 2020; 38: 2101-2105.
[16] Sievert KD, Daum L, Maurer S, Toomey P, Vaegler M, Aufderklamm S and Amend B. Urethroplasty performed with an autologous urothelium-vegetated collagen fleece to treat urethral stricture in the minipig model. World J Urol 2020; 38: 2123-2131.
[17] Coplen DE. Tissue-engineered autologous urethras for patients who need reconstruction: an observational study. Yearbook of Urology 2011; 2011: 175-176.
[18] Simões IN, Vale P, Soker S, Atala A, Keller D, Noiva R, Carvalho S, Peleteiro C, Cabral JM, Eberli D, da Silva CL and Baptista PM. Acellular urethra bioscaffold: decellularization of whole urethras for tissue engineering applications. Sci Rep 2017; 7: 41934.
[19] Zhang K, Fu Q, Yoo J, Chen X, Chandra P, Mo X, Song L, Atala A and Zhao W. 3D bioprinting of urethra with PCL/PLCL blend and dual autologous cells in fibrin hydrogel: an in vitro evaluation of biomimetic mechanical property and cell growth environment. Acta Biomater 2017; 50: 154-164.
[20] Zhou S, Yang R, Zou Q, Zhang K, Yin T, Zhao W, Shapter JG, Gao G and Fu Q. Fabrication of tissue-engineered bionic urethra using cell sheet technology and labeling by ultrasmall superparamagnetic iron oxide for full-thickness urethral reconstruction. Theranostics 2017; 7: 2509-2523.
[21] Fan S, Zheng X, Zhan Q, Zhang H, Shao H, Wang J, Cao C, Zhu M, Wang D and Zhang Y. Super-strong and intrinsically fluorescent silkworm silk from carbon nanodots feeding. Nanomicro Lett 2019; 11: 75.
[22] Yao J, Chen S, Chen Y, Wang B, Pei Q and Wang H. Macrofibers with high mechanical performance based on aligned bacterial cellulose nanofibers. ACS Appl Mater Interfaces 2017; 9: 20330-20339.