# THE ASSOCIATION BETWEEN COLLAGEN, INFLAMMATION, AND FIBROSIS WITH MAXIMUM URINARY FLOW RATE IN HYPOSPADIAS PATIENTS AFTER URETHROPLASTY

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*ABSTRACT*

***Introduction:*** *Hypospadias repair may cause long-term urinary dysfunction. Collagen, inflammation, and fibrosis may influence urethral healing and urinary flow, but their association with postoperative Qmax remains unclear.* ***Objective:*** *This study aims to investigate the relationship between collagen, inflammation, and fibrosis with maximum urinary flow rate in patients with hypospadias after urethroplasty.* ***Material &Methods:*** *This retrospective cohort study included 72 hypospadias patients who underwent surgery at Ngoerah General Hospital, Denpasar, from 2003 to 2013. Urethral tissue samples were histopathologically assessed for collagen, inflammation, and fibrosis. Urinary flow was evaluated 10 years postoperatively using uroflowmetry, with Qmax categorized based on the optimal ROC-derived cutoff. Associations were analyzed using chi-square and logistic regression.* ***Results:*** *The results showed a significant association between collagen and maximum urinary flow rate (RR=0.573; 95% CI=0.350–0.936; p=0.019), where low collagen levels were protective against weak urinary stream. Moderate-to-severe fibrosis increased the risk of weak urinary stream by 1.6 times (RR=1.659; 95% CI=1.071–2.568; p=0.026). However, no significant association was found between inflammation and maximum urinary flow rate (p=0.964). Logistic regression analysis indicated that patient age was significantly associated with maximum urinary flow rate (OR=1.32; p=0.002).****Conclusion:*** *There is an association between collagen levels and maximum urinary flow rate in patients after hypospadias surgery. However, no significant association was found between inflammation and fibrosis with urinary flow. Patient age was the dominant factor influencing urinary flow post-surgery.*

***Keywords:*** *Collagen, inflammation, fibrosis, maximum urinary flow rate, urethroplasty.*

***ABSTRAK***

***Pendahuluan:*** *Tindakan perbaikan hipospadia dapat menyebabkan gangguan fungsi saluran kemih jangka panjang. Kolagen, peradangan, dan fibrosis dapat memengaruhi penyembuhan uretra serta aliran urine, namun kaitannya dengan nilai Qmax pasca operasi masih belum jelas.****Tujuan:*** *Penelitian ini bertujuan untuk mengetahui hubungan antara kolagen, inflamasi, dan fibrosis dengan pancaran kencing maksimal pada pasien hipospadia pasca-uretroplasti.* ***Bahan &Cara:*** *Studi kohort retrospektif ini melibatkan 72 pasien hipospadia yang menjalani pembedahan di RSUP Ngoerah, Denpasar, antara tahun 2003 dan 2013. Sampel jaringan uretra diperiksa secara histopatologis untuk menilai kandungan kolagen, peradangan, dan fibrosis. Aliran urine dievaluasi 10 tahun pasca operasi menggunakan uroflowmetri, dengan nilai Qmax dikategorikan berdasarkan titik potong optimal yang diperoleh melalui analisis ROC. Analisis hubungan antar variabel dilakukan menggunakan uji chi-square dan regresi logistik.* ***Hasil:*** *Hasil penelitian menunjukkan bahwa terdapat hubungan signifikan antara kolagen dengan pancaran kencing maksimal (RR = 0,573; 95% CI = 0,350-0,936; p = 0,019), di mana kolagen rendah merupakan faktor protektif terhadap pancaran kencing lemah. Fibrosis sedang-berat meningkatkan risiko pancaran kencing lemah sebesar 1,6 kali (RR = 1,659; 95% CI = 1,071-2,568; p = 0,026). Namun, tidak ditemukan hubungan signifikan antara inflamasi dengan pancaran kencing maksimal (p = 0,964). Regresi logistik menunjukkan bahwa usia pasien berhubungan signifikan dengan pancaran kencing maksimal (OR = 1,32; p = 0,002).****Simpulan:****Terdapat hubungan antara tingkat kolagen dan pancaran kencing maksimal pada pasien hipopasdia pasca operasi hipospadia, namun tidak ditemukan hubungan signifikan antara inflamasi dan fibrosis dengan pancaran kencing maksimal. Usia pasien merupakan faktor dominan yang mempengaruhi pancaran kencing pasca operasi.*

***Kata kunci:*** *Kolagen, inflamasi, fibrosis, pancaran kencing, uretroplasti.*

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## INTRODUCTION

Hypospadias is one of the most commonly encountered congenital anomalies in pediatric urology. It is defined as a condition in which the meatus urethrae externus (MUE) is not located at the tip of the penis but rather on the ventral aspect of the penile shaft.[1] The prevalence of hypospadias is approximately 1 in 250 live births.[2] According to a multicenter study conducted across 12 tertiary pediatric urology referral centers in Indonesia, there were 591 reported cases of hypospadias in 2017. At NgoerahGeneral Hospital Denpasar, 83 cases were documented during the same year.[3]

Hypospadias repair is a technically challenging surgical procedure and may result in various complications, such as a weak urinary stream, unsatisfactory penile cosmesis, residual penile curvature, urethrocutaneous fistula, meatal stenosis, and entrapped penis.[4-5] Postoperative outcomes of hypospadias repair can be evaluated using several methods, one of which is the maximum urinary flow rate (Qmax) assessed through uroflowmetry. According to Piplani et al. (2018), 43% of patients experienced a weak urinary stream nine months after undergoing hypospadias surgery. Several factors may influence surgical outcomes, including the type of hypospadias, age at the time of surgery, surgical technique used, surgeon's expertise, preoperative hormonal therapy, wound care technique, and type of suture material employed.[4,6-8]

The microstructural components, such as collagen, inflammation, and fibrosis, play significant roles in the healing process following hypospadias repair. The mechanism by which inflammation contributes to reduced urinary flow is thought to involve increased expression of cyclooxygenase-2 (COX-2) and degradation of nuclear factor kappa B (NF-κB), leading to the accumulation of fibroblasts and rigid type I collagen. This impairs urinary flow by reducing tissue elasticity. Elevated levels of type I collagen displace the more elastic type III collagen, resulting in a decreased type III:I collagen ratio. Tissue fibrosis compromises organ function by replacing normal tissue with scar tissue that is rich in type I collagen but low in type III collagen, thereby increasing tissue stiffness and reducing its elasticity and compliance. Inflammation may also disrupt normal tissue innervation and vascularization, further impairing urinary stream.[9] Collagen is also hypothesized to influence the surgical outcomes of hypospadias. Type III collagen has been found to be more abundant in children compared to adults, and this higher concentration is hypothesized to contribute to better surgical outcomes in pediatric patients. With aging, there is a natural decline in type III collagen and an increase in type I collagen, which leads to a reduction in the type III:I collagen ratio, potentially worsening surgical outcomes.[10]

Studies on the long-term outcomes of patients following hypospadias repair and the factors influencing these outcomes are essential for predicting patient prognosis. One of the key long-term outcomes is urinary stream quality, which can be objectively assessed using uroflowmetry. Proximal hypospadias has been identified as a risk factor for weak urinary stream in patients who have undergone tubularized incised plate (TIP) urethroplasty.[11] If fibrosis, collagen deposition, and inflammatory processes are found to significantly influence postoperative urinary stream, this could serve as a foundation for the development or application of targeted therapies, such as anti-inflammatory agents or collagen-modulating treatments. Previous studies have explored the roles of inflammation, fibrosis, and collagen in other urological conditions, such as benign prostatic hyperplasia (BPH) and urethral stricture, but no such studies have yet been conducted specifically in postoperative hypospadias patients. Based on this gap in the literature, the researchers are interested in investigating the potential relationship between patients following hypospadias repair.

## OBJECTIVE

This study aims to investigate the relationship between collagen, inflammation, and fibrosis with maximum urinary flow rate in patients with hypospadias after urethroplasty.

## MATERIAL & METHODS

This study is an analytical observational study employing a retrospective cohort design. It

involved the evaluation of collagen, inflammatory response, and fibrosis based on histopathological analysis of paraffin-embedded tissue blocks collected during hypospadias surgery. Postoperative urinary flow outcomes were assessed 10 years after surgery, with patients categorized into low and normal maximum urinary flow rate (Qmax) groups, based on the optimal cutoff determined by the receiver operating characteristic (ROC) curve. The study population consisted of hypospadias patients who underwent surgical repair at Ngoerah General Hospital in Denpasar between 2003 and 2013, and who met the specified inclusion and exclusion criteria. Subjects were selected using simple random sampling with a random number generator.

The inclusion criteria for this study were all patients with hypospadias who underwent surgical repair at Ngoerah General Hospital, performed by Gede Wirya Kusuma Duarsa, Pediatric Urology Specialist, with histopathological examination conducted at least six months prior to the urinary flow assessment. Exclusion criteria included damaged paraffin tissue blocks, incomplete medical records, patients who underwent reoperative hypospadias surgery, surgeries performed by a different surgeon, patients who experienced postoperative infection and/or wound dehiscence, and patients who refused to participate or failed to attend follow-up appointments.This study was conducted following the approval of the ethics committee of the Research and Development Unit, Faculty of Medicine, Udayana University/Ngoerah General Hospital Denpasar, and with formal permission from the Hospital Director to access patient medical records.

The variables assessed in this study included urinary stream (Qmax), collagen, inflammation, age at the time of surgery, and type of hypospadias. Maximum urinary flow rate (Qmax) was evaluated using uroflowmetry. Inflammation and fibrosis were assessed through histopathological examination of urethral plate tissue obtained during surgery, using Hematoxylin-Eosin (HE) and Masson's Trichrome staining. Collagen was evaluated specifically using Masson's Trichrome staining. Statistical analysis for comparison of proportions was performed using the Chi-square test, followed by logistic regression analysis using SPSS version 25.0.

## RESULT

This study included a total of 100 hypospadias patients who underwent surgery at Ngoerah General Hospital in Denpasar between 2003 and 2013. Of these, 72 subjects met the inclusion and exclusion criteria and were included in the analysis. The characteristics of the study subjects are presented in Table 1.

The cut-off value for maximum urinary flow rate (Qmax) was determined using a Receiver Operating Characteristic (ROC) curve. The ROC analysis revealed that the Qmax cut-off for inflammation was 10.9 mL/s, for fibrosis was 10.35 mL/s, and for collagen deposition was 9.95 mL/s (Table 2). The ROC curves for each variable are presented in Figure 1.

**Table 1**. Study Subject Characteristics.

| Variable | Mean ± SD | Median (IQR) | Mode | Min | Max |
|---|---|---|---|---|---|
| Age (Years) | 6.27±3.99 | 5 (4-7.8) | 4 | 2 | 26 |
| Degree of curvature | | | | | |
| Mild | | 28 (38.9) | | | |
| Moderate | | 18 (25.0) | | | |
| Severe | | 26 (36.1) | | | |
| Volume (ml) | 142.82±69.5 | 123.5 (99.9-174) | 110 | 21 | 383 |
| Time (second) | 35.08±93.25 | 24 (16.4-29.5) | 24 | 4.3 | 809 |
| Qmax (ml/second) | 11.36±4.43 | 10.5 (8.7-12.8) | 5.6 | 4.2 | 30.6 |

**Table 2**. Cut-off value of maximum urinary glow rate (Qmax).

| Variable | AUC | Sensitivity | Specificity | Cutoff | p | 95%CI |
|---|---|---|---|---|---|---|
| Collagen | 0.642 | 60% | 62.2% | 10.9 | 0.038 | 0.514-0.770 |
| Fibrosis | 0.394 | 43.3% | 42.9% | 10.35 | 0.129 | 0.256-0.533 |
| Inflammation | 0.529 | 55.6% | 48.7% | 9.95 | 0.691 | 0.381-0.677 |

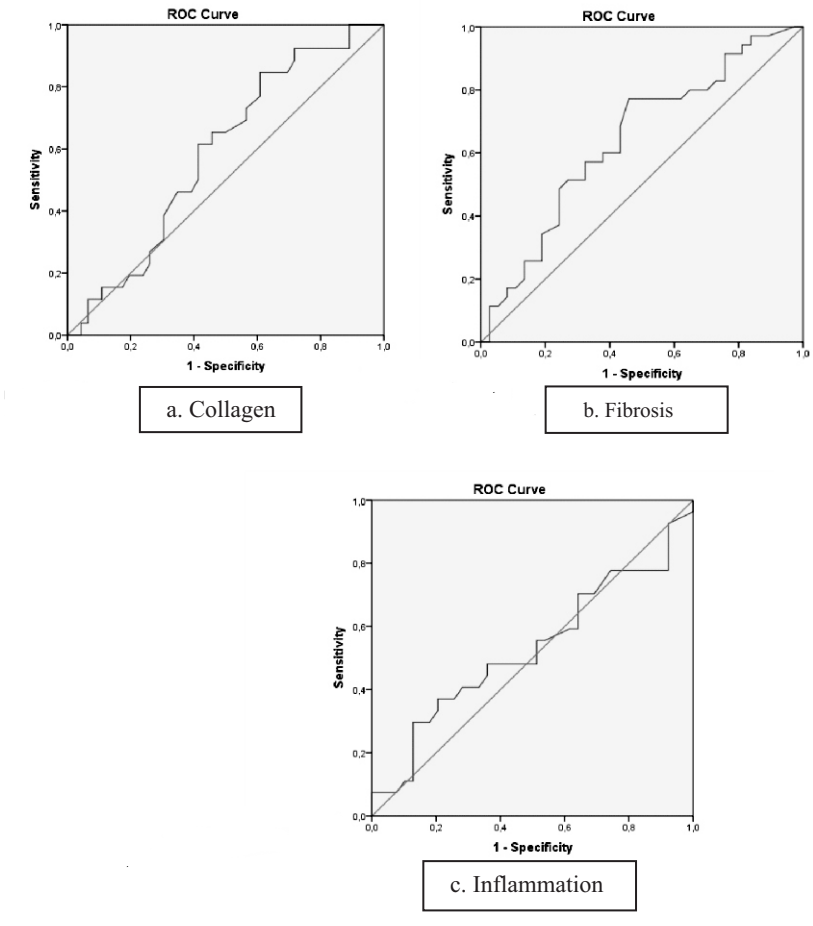


**Figure 1.** Depicts three Receiver Operating Characteristic (ROC) curves labeled "a," "b," and "c." These curves illustrate the trade-off between sensitivity (True Positive Rate) and 1-specificity (False Positive Rate) at various threshold settings.

The association between collagen, inflammation, and fibrosis with maximum urinary flowrate (Qmax) was analyzed using the Chi-square test. The results showed a significant association between collagen levels and urinary flow, where low collagen was found to be a protective factor against weak urinary flow (RR = 0.573; 95% CI = 0.350–0.936; p = 0.019). In addition, a significant association was observed between fibrosis severity and urinary flow, where moderate to severe fibrosis increased the risk of weak urinary stream by 1.6 times compared to mild fibrosis (RR = 1.659; 95% CI = 1.071–2.568; p = 0.026). No significant association was found between inflammation and urinary flow (Table 3).

The relationship between collagen, inflammation, and fibrosis with maximum urinary flow was analyzed using logistic regression analysis. The results of the logistic regression test can be seen in Table 5.4, where only age was significantly associated ($p < 0.05$), with an odds ratio (OR) of 1.32. The explanatory power of the independent variables for the dependent variable was 28%, with a prediction accuracy of 75.8%. To determine the most dominant variable, further analysis was conducted. The initial step was to assess the model fit based on the logistic regression results in Table 4. The feasibility analysis showed that only age and collagen met the criteria for multivariate analysis, with p-values $\leq 0.25$, while variables with $p > 0.25$ were deemed unsuitable for inclusion in the regression analysis. The results of the repeated regression analysis showed that age was the most dominant factor significantly associated with urinary flow ($p < 0.05$), with an odds ratio (OR) of 1.32 (Table 5).

**Table 3.** Association between collagen, inflammation and fibrosis with maximum urinary flow rate.

| | Urinary Flow Rate(Qmax) | | P value | RR | 95% CI |
|---|---|---|---|---|---|
| | Weak | Normal | | | |
| Collagen | | | | | |
| Low | 13 (37.1) | 22 (62.9) | 0.019 | 0.573 | 0.350-0.936 |
| High | 24 (64.9) | 13 (35.1) | | | |
| Fibrosis | | | | | |
| Mild | 19 (63.3) | 9 (32.1) | 0.026 | 1.659 | 1.071-2.568 |
| Moderate-Severe | 18 (40.9) | 26 (59.1) | | | |
| Inflammation | | | | | |
| No | 20 (51.3) | 19 (48.7) | 0.964 | 0.989 | 0.615-1.590 |
| Yes | 14 (51.9) | 13 (48.1) | | | |

**Table 4.** Result of the logistic regression test.

| Variable | B | S.E. | Wald | p value | Exp (B) | Confidence Interval 95% | |
|---|---|---|---|---|---|---|---|
| | | | | | | Above | Below |
| Age | 0.278 | 0.095 | 8.557 | 0.003 | 1.321 | 1.096 | 1.591 |
| Collagen | -0.602 | 0.352 | 2.928 | 0.087 | 0.548 | 0.275 | 1.091 |
| Fibrosis | -0.175 | 0.321 | 0.298 | 0.585 | 0.839 | 0.447 | 1.574 |
| Inflammation | -0.337 | 0.585 | 0.331 | 0.565 | 0.714 | 0.227 | 2.248 |
| Degree of Chordee | 0.080 | 0.320 | 0.063 | 0.802 | 1.083 | 0.579 | 2.028 |

**Table 5.** The association between age and collagen with maximum urinary flow.

| Variable | B | S.E. | Wald | p value | OR |
|---|---|---|---|---|---|
| Age (year) | .277 | .091 | 9.241 | .002 | 1.319 |
| Collagen | .644 | .335 | 3.701 | .054 | .525 |

## DISCUSSION

This study demonstrated that the median age of hypospadias patients undergoing surgical repair at Ngoerah General Hospital was 5 years. A study by Duarsa and Nugroho (2016) reported that the median age of hypospadias patients who underwent surgery at Ngoerah General Hospital (formerly Sanglah General Hospital) from January 2009 to April 2012 was 7.35 years, with the youngest patient being 2 years old and the oldest 17 years old. Based on a multicenter study conducted in 12 tertiary pediatric urology referral hospitals in Indonesia, the majority of patients were older than 4 years.[3] In another study from the United Kingdom, the average age of children at the time of hypospadias repair was reported to be 2.5 years.[12]

In the present study, age was found to be significantly associated with maximum urinary stream (Qmax). The American Academy of Pediatrics recommends that hypospadias repair be performed between the ages of 6 and 12 months to prevent psychological consequences that may occur after the age of 18 months. Ziada et al. (2011) found a significantly higher complication rate in patients who underwent surgery at an older age compared to

those operated on between 6-12 months.[13] Similarly, studies by Dale et al. (2023) and Garnier et al. (2017) also reported that the complication rate in hypospadias repair was higher in patients operated on at an older age. This may be attributed to increased expression of age-related pro-inflammatory cytokines by fibroblasts, which are believed to negatively impact wound healing and postoperative outcomes.[12,14] Furthermore, in older hypospadias patients who have developed pubic hair, the hair may serve as a reservoir for infection, making it more prone to harbor bacterial colonization compared to prepubescent patients without pubic hair. This may further explain the elevated complication rates observed in older patients. One such complication, urethral stricture, can lead to impaired urinary flow or reduced urinary stream (Qmax).[5]

In older children and adults, the penile skin and tissues are also found to be less pliable due to a decreased Type III to Type I collagen ratio, making it more challenging to achieve satisfactory cosmetic outcomes. The risk of complications, such as fistula formation and stricture, may be higher in older patients due to reduced tissue vascularization and delayed healing potential.[10,15]

Contrasting findings were reported by Bush et al. (2023), who stated that there was no significant association between age at the time of hypospadias surgery and surgical outcomes. Although increased pro-inflammatory cytokine production and a decreased Type III:I collagen ratio may occur in older patients, younger infants may be at greater risk for anesthesia-related complications due to their physiological immaturity. In contrast, older children and adults may tolerate general anesthesia better, and a larger penile size can facilitate the surgical procedure, potentially allowing for more favorable cosmetic results.[16]

The median maximum urinary flow rate (Qmax) in this study was 10 mL/second. A study by Saksono and Duarsa (2017) reported that the normal Qmax value in the pediatric population is >10 mL/second, with a median Qmax of 9.54 mL/second in patients with proximal hypospadias, and 22.49 mL/second in those with distal hypospadias.[8] Another study reported that the mean Qmax in patients prior to hypospadias repair was 6.20±0.42 mL/second, increasing to 8.53±0.42 mL/second at 3 months, 11.18±0.47 mL/second at 6 months, and 13.71±0.44 mL/second at 1 year postoperatively.[16]

This study found that low collagen levels were a protective factor against reduced maximum urinary flow (Qmax). However, this study did not identify whether the decrease was in Type I or Type III collagen. Elevated Type I collagen and reduced Type III collagen can increase tissue stiffness, thereby reducing tissue elasticity and compliance, including during micturition. An increase in Type I collagen also displaces the more elastic Type III collagen, lowering the Type III:I collagen ratio. Excessive collagen deposition and disorganized collagen fibers within the urethra may lead to urethral stricture. Urethral stricture causes narrowing or obstruction of the urethral lumen, which in turn increases urinary outflow resistance and reduces maximum urinary flow rate.[9]

Collagen is the primary structural protein in the extracellular matrix (ECM) of the urethra and plays a critical role in wound healing and tissue remodeling following hypospadias repair. Collagen is also hypothesized to influence surgical outcome in hypospadias. Type III collagen is more abundant in children compared to adults, and it is hypothesized that this abundance contributes to better surgical outcomes in pediatric patients. With aging, there is a decline in Type III collagen and an increase in Type I collagen, leading to a decreased Type III:I collagen ratio.[10,15]

An immunohistochemistry-based study found Type I and IV collagen subtypes in the urethral plate of patients with hypospadias and moderate-to-severe chordee, but Type III collagen was not detected. A study by Yuri et al. (2020) in Indonesia reported that Type III collagen expression, as measured by qPC, was significantly decreased in patients with moderate and severe hypospadias compared to those with mild forms. A study by Jinjin Ma (2012) reported that tissues from men with lower urinary tract symptoms (LUTS) were significantly stiffer ($p = 0.0016$), had a higher collagen content ($p = 0.0038$), and lower glandular density than tissues from men without LUTS.[10]

This study found that fibrosis was a significant risk factor for reduced maximum urinary flow rate (Qmax) in the multivariate analysis. However, after controlling for age and degree of chordee, fibrosis was no longer significantly associated with maximum urinary flow. A retrospective multicenter cohort study by Subnafeu and Duarsa reported that fibrotic tissue in the urethra was significantly correlated with patient's Qmax values.[17]

Tissue fibrosis impairs organ function by

replacing normal tissue with scar tissue characterized by high Type I collagen and low Type III collagen, leading to increased tissue stiffness. Elevated Type I collagen displaces the more elastic Type III collagen, resulting in a decreased Type III:I collagen ratio. Accumulation of fibroblasts and rigid Type I collagen can obstruct urinary flow.[18]

Fibrosis in the urethral tissue can cause loss of elasticity and compliance, rendering the urethra less distensible. During micturition, the urethra needs to dilate to accommodate increased urine flow. If the urethra is less compliant due to fibrosis, it cannot adequately dilate, leading to increased resistance and a decreased maximum urinary flow rate. Fibrosis may also disrupt the normal architecture and function of smooth muscle in the urethra, which plays a critical role in facilitating urinary flow. Dysfunction of the smooth muscle can cause inadequate urethral relaxation and dilation during urination, further contributing to reduced Qmax. Additionally, fibrotic tissue formation may interfere with normal innervation of the urethra, affecting the coordination of the urethral sphincter and smooth muscle function. Impaired neural control can result in inefficient urethral muscle relaxation and contraction, causing suboptimal urinary flow dynamics.[18,19]

This study found no association between inflammation and maximum urinary flow. This is likely because the majority of hypospadias patients in this study had only mild or no inflammation, and there were no samples with moderate or severe inflammation. A study by Zhang et al. reported that inflammation in both tissue biopsies and serum was significantly associated with Qmax values. Patients without tissue inflammation demonstrated better Qmax outcomes 12 months postoperatively.[20] This finding is consistent with a study by Li et al., which showed that patients with inflammation detected in prostate tissue biopsies, based on hematoxylin and eosin staining and elevated serum inflammatory biomarkers had lower Qmax values.

The mechanism by which inflammation reduces urinary flow is hypothesized to involve increased expression of COX-2 and degradation of NF-?B, which may lead to the accumulation of fibroblasts and stiff Type I collagen, thereby impeding urine flow. Inflammation is also recognized as a causative factor for fibrosis, characterized by myofibroblast accumulation, collagen deposition, ECM remodelin, and increased tissue stiffness.[9]

## CONCLUSION

Various factors can influence urinary flow following hypospadias surgery, one of which is collagen, as demonstrated in this study. No association was found between the degree of inflammation or fibrosis and urinary flow postoperatively. These findings may provide a basis for developing or applying collagen-based therapies in patients with hypospadias. Further research is warranted to identify which collagen types (Type I, Type II, Type III, and Type IV) affect maximum urinary flow as well as the Type I:III collagen ratio.

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