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Histopathology of Anterior Urethral Strictures: Towards a Better Understanding of Stricture Pathophysiology

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Abstract

Introduction: Histopathology can provide insights into disease mechanism, but to date has been poorly described in urethral strictures. The purpose of this study was to comprehensively describe the histopathologic findings from stricture specimens obtained at the time of anterior urethroplasty (AU).

Methods: All pathologic specimens from men undergoing AU for USD from 2010–2017 at a single institution were re-reviewed by a single, blinded pathologist who was directed to rule out lichen sclerosus (LS) and then describe inflammatory cell type and severity when present. Cohorts comprised of strictures with no inflammation, minimal to mild inflammation, or moderate to severe inflammation were developed and stricture, patient and surgical outcome characteristics were compared.

Results: Histopathology slides from 100 AU cases were reviewed. Two or more LS characteristics were present in 21% of specimens and 44% of specimens showed chronic inflammation (minimal 20%, mild 39%; moderate 39%; severe 2%). Lymphocytes (86%) and plasma cells (12%) were the predominant cell type. Patients with inflammatory strictures reported worse overall health. Inflammation was largely absent from isolated bulbomembranous strictures (9%) and more common in LS strictures (100%). The overall failure rate of 11% was not affected by the presence (7%) or absence (14%) of inflammation.

Conclusions: Chronic inflammation is prevalent in a significant percentage of USD specimens. Associations with worse overall health suggest systemic mediators. Absence of inflammation in bulbomembranous strictures suggests a unique pathophysiology in this region. The presence of inflammation did not affect surgical outcomes at medium-term follow-up.

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Keywords

Urethral Stricture Disease; Histopathology; Chronic Inflammation; Pathophysiology; Lichen Sclerosus

Introduction:

The foundation for pursuit of all medical advancement begins with a sound understanding of the fundamentals of the disease process in question. In diseases directly affecting organs, that understanding usually begins by analyzing the histopathology. Currently, there exists a paucity of studies that have focused specifically on the histopathology of urethral stricture disease (USD), with most that do studying only the collagen distribution within the extracellular matrix^{1–3}. This focus is predicated on the assumption that USD is a disorder of fibrosis and scarring of the urethra.

More recently, as chronic inflammation is increasingly implicated in systemic, chronic diseases^{4, 5}, the role of inflammation is also being explored in USD development^{6, 7}. Lichen sclerosus (LS), an inflammatory genital skin condition known to affect the urethra and cause strictures, appears to occur more commonly in men with concomitant systemic inflammatory conditions (e.g. metabolic syndrome)⁸. Furthermore, pathology of the strictures that develop in these men show chronic inflammation^{9–12} and, accordingly, appear to respond early in the disease process to local corticosteroid treatments¹³. Importantly, inflammation is also being recognized as a component of non-LS strictures⁷, implying that USD may be more of an active process (and therefore, potentially reversible) than had been previously appreciated.

The purpose of our current study was three-fold. First, we sought to evaluate USD pathology specimens in the context of chronic inflammation characterization (rather than dysplasia), to determine baseline histopathology heterogeneity. Second, we sought to determine if stricture characteristics, patient demographics, and patient reported outcomes measures (PROM) differed in patients found to have inflammatory versus non-inflammatory strictures. Finally, we sought to determine how the presence of chronic inflammation in the stricture affected surgical outcomes.

Materials/Methods:

All men undergoing anterior urethroplasty from 2010–2017 at a single institution in which tissue was obtained at the time of surgery were initially included in the study. Patients with history of urethrotomy performed within 3 months of the urethroplasty and/or those actively performing intermittent catheterization were excluded.

Pathology Review

The original pathology reports prepared for the surgical specimens (originally sent to rule out the presence of dysplasia and/or malignancy) were reviewed to determine if the pathologist had included any of the following findings: presence/absence of 1) hyperkeratosis, 2) thinning/thickening of epithelium, 3) degeneration of the basal cell layer,

4) dermal collagen homogenization, or 5) lichenoid lymphocytic or plasmacytic infiltrate. Notably, these five criteria were chosen as they are common characteristics used in the diagnosis of lichen sclerosus and were also the same used in a study by Liu. et al., in which the authors determined that the presence of two or more of these characteristics constituted LS⁷. The original slides were then re-reviewed by a single, blinded pathologist (LD), not involved in the study design, who was directed to “rule out LS” using the same five criteria above. Additionally, the pathologist was asked to determine the presence or absence of inflammation. If inflammation was present the pathologist classified this as acute vs chronic and determined the predominant cellular infiltrate (e.g. neutrophils, lymphocytes, plasma cells, eosinophils). The pathologist then graded the severity of the inflammation as none, minimal, mild, moderate, or severe based on a grading system that is utilized in the BPH literature (Appendix 1).

Once pathology specimens had been rereviewed, three cohorts were created comprised of patients with no inflammation, minimal to mild inflammation, or moderate to severe inflammation present in the stricture on the final review. A prospectively maintained, IRB approved database was then utilized to obtain information on patient and stricture characteristics, as well as pre-operative patient reported outcomes measures. Surgical success, defined as both the ability to traverse the reconstructed urethra with a flexible cystoscope at routine follow-up or need for procedural intervention, was determined using both the database and a comprehensive, institution specific chart review. Stricture locations were defined by their most distal extent (e.g. a stricture extending from the proximal to distal bulb was labeled “distal bulbar”). Post-operative complications occurring within 90 days of surgery were classified according to the Clavien-Dindo system and reported if Clavien grade 2¹⁴.

Statistical Analysis

Descriptive statistics were utilized to summarize the patient demographics and pathologic characteristics of stricture specimens both before and after re-review. Cohort stricture characteristics, patient demographics and PROMs were then compared using student's *t*-test or ANOVA for continuous variables and Chi-square analysis for categorical variables. A *p*-value of <0.05 constituted statistical significance.

Results:

We analyzed 100 consecutive cases of anterior urethroplasty in which pathologic specimens were obtained and sent for pathologic analysis between 8/2010 and 5/2017. During this time period an additional 135 anterior urethroplasties were performed in which tissue was not analyzed. Table 1 provides a summary of patient characteristics, stricture characteristics, and stricture management. The average patient age was 41.5 years and the average stricture length was 2.6 cm. The majority of strictures were idiopathic (43%) and isolated in the bulbar urethra (78%). Excision and primary anastomosis urethroplasty (EPA) was performed in 66 patients, non-transecting (spongiosus sparing with mucosal excision) anastomotic repair in 15 patients, augmented anastomotic substitution urethroplasty in 13 patients, and other urethral reconstructive procedures in 6 patients.

The results of the primary and pathologic re-review are summarized in Table 2. Re-review identified significantly higher numbers of pathologic specimens with hyperkeratosis (36 versus 14 specimens, $p=0.0005$), and subepithelial hyalinization (8 specimens versus 1 specimen, $p=0.035$). On initial pathology review 6 patients (6%) had two or more pathologic criteria associated with LS compared to 21 patients (21%) on re-review ($p=0.0004$). Of these 21 strictures, 16 (76%) were bulbar, 4 (19%) were penile, and 1 (5%) was multifocal. No bulbomembranous strictures displayed histopathologic features associated with LS. There were 44 specimens with pathologic chronic inflammation present, of which 9 (20%) were graded as minimal, 17 (39%) as mild, 17 (39%) as moderate, and 1 (2%) as severe (Table 3). Histopathologic images and retrograde urethrograms representing the observed spectrum of chronic inflammation severity are depicted in Figure 1. The large majority of inflammatory specimens displayed a lymphocytic predominant cellular infiltrate (38 specimens, 86%) with the remainder consisting of plasma cell (5 specimens, 12%), and neutrophilic infiltrates (1 specimen, 2%).

Clinical and stricture characteristics, prior management, urethroplasty technique, and surgical outcomes of patients with non-inflammatory ($n=56$), minimal to mild ($n=26$), and moderate to severe inflammatory strictures ($n=18$) were compared and summarized in Table 4. Compared to patients with non-inflammatory strictures, those with chronic inflammation present were more likely have a clinical diagnosis of genital LS ($p=0.007$). Despite similar stricture length and etiology, inflammatory strictures were nearly absent from the bulbomembranous urethra ($n=1$, 2.3%). Prior stricture intervention and urethroplasty techniques were similar between groups. Rates of post-operative complication Clavien 2 within 90 days and stricture recurrence, as defined by both the inability to pass the flexible cystoscope and need for procedural intervention, were similar at mean follow up of 25 months.

A total of 37 (37%) patients completed a validated, urethroplasty specific questionnaire pre-operatively¹⁵, and those patients with inflammatory ($n=17$) and non-inflammatory strictures ($n=20$) were compared (Table 5). Patients with inflammatory strictures had significantly lower average overall health scores (77.8 vs 67.2, $p=0.04$) but were similar with regards to all other urinary symptom and health status domains.

Discussion:

This study of 100 consecutive urethral stricture specimens revealed several important findings regarding urethral stricture histopathology. First, routine pathologic analysis of USD specimens fails to fully capture stricture heterogeneity, especially as it pertains to urethral inflammation. Second, nearly 50% of stricture specimens showed evidence of pathologic chronic inflammation. Patients with these inflammatory strictures reported significantly worse overall health, implying an association between systemic disease and the development of inflammatory strictures, 44% of which were deemed idiopathic in our study. Third, chronic inflammation was largely absent from the strictures involving the bulbomembranous urethra, potentially indicating a distinct pathophysiology in these strictures. Finally, though chronic inflammation was higher than expected in USD

specimens, its presence was not shown to impact urethroplasty success rates, although the study was likely underpowered to detect this difference.

Male urethral stricture disease (USD) has an estimated prevalence of 0.6% and for most affected men is a bothersome and painful chronic medical condition causing significant urologic and sexual morbidity¹⁶. Despite the clear clinical heterogeneity of USD its underlying pathophysiology remains poorly understood, with 50–70% of all strictures deemed idiopathic/unknown¹⁷. Accordingly, pathophysiology rarely directs treatment for USD, with most surgeons electing either endoscopic and/or open surgical treatments that aim to restore urethral patency, regardless of etiology. The high reported success rates of urethral reconstruction, ranging from 70–99% after anterior urethroplasty, are likely discouraging further work into a more comprehensive understanding of USD pathophysiology¹⁸. However, this apathy towards a deeper understanding of USD prevents further clinical advancements and implies we have reached the pinnacle of therapeutics for this disease, which is likely not the case.

Prior studies of USD histopathology have mostly focused on the extracellular matrix and collagen makeup, as USD is generally considered to be a fibrotic disorder. One study identified differences in the glycosaminoglycan composition of the extracellular matrix in patients with urethral strictures compared to healthy controls, with strictured segments having lower concentrations of hyaluronic acid and higher concentrations of dermatan sulfate, suggesting that these strictured areas were in a later stage of wound healing (and also implicating a prior injury as the cause of the stricture)². Similarly, the impact of extracellular matrix changes on the density and type of collagen fibers, vascular density, and elastic fibers has been studied in the context of scarring and the role that fibrosis modifiers may have on the treatment of urethral stricture disease¹. However, organ fibrosis is often the end-stage of chronic inflammatory processes and is a mostly irreversible process¹⁹. Thus, targeting the inflammatory process, rather than the fibrosis, of USD may be the most beneficial way to develop and improve non-urethroplasty treatment methods as has been suggested in distal LS strictures^{13, 20}

Our pathologic re-review identified both a significantly higher number of pathologic features associated with LS than were described on the original pathology report as well as a high prevalence of chronic inflammation. These findings are similar to a study by Liu and colleagues in which pathologic re-review of bulbar strictures identified two or more features characteristic of LS in 44% of patients compared to 7% on primary review⁷. Applying the same criteria, we also identified a significant increase of LS features from 6 (6%) on primary review to 21 specimens (21%) on secondary review ($p=0.004$). While the Liu study examined only bulbar strictures, we identified these LS features throughout the urethra with the notable exception of the bulbomembranous urethra which was spared from these histologic changes. Notably all four patients with dermatologic LS had involvement of the penile urethra and also displayed histologic features of LS. We propose that these histopathologic findings, in the absence of genital LS changes, do not represent true LS, but rather, are suggestive of a poorly understood chronic inflammatory process that seems to spare the most proximal bulbar urethra.

Chronic inflammation in USD has been previously studied in the context of prior gonococcal urethritis. In a 1977 autopsy study of 11 patients with gonococcal USD, the authors noted that while stricture specimens were characterized by dense hyalinized scar, they also displayed mucosal and sub-mucosal inflammation many years after the acute urethritis had resolved, indicating the presence of a persistent, unknown antigenic mediator²¹. A separate pathologic study of 107 patients with post-inflammatory strictures undergoing 2-stage repairs confirmed the presence of chronic inflammation in the stricture segment, but also in non-strictured segments immediately adjacent to the narrowed area²². This finding suggests that the inflammatory process can exist independent of any anatomic narrowing or voiding impairment, and furthermore, that stricturing (fibrosis) of the urethra may simply be the end stage of the local inflammatory process.

The presence of systemic inflammation may also be playing a role in the presence of local/focal urethral inflammation and possibly in stricture pathophysiology. Studies focusing on lichen sclerosus USD patients have identified higher than expected rates of chronic inflammatory conditions such as diabetes and hypertension^{6, 8}. In our study, we also noted that men with inflammatory strictures reported worse overall health. While these associations are not causative, they seem to again confirm that chronic inflammation within the urethra may, in some cases, be a local manifestation of a systemic disease process – and furthermore, a more comprehensive understanding of urethral inflammation may offer clues into pathophysiology and potentially, better medical and surgical treatments.

The lack of chronic inflammation in short strictures confined to the bulbomembranous urethra was an unexpected finding that cannot be fully explained. Often strictures in this location are attributed to history of urethral trauma, however in our study 8 of the 11 bulbomembranous strictures (72%) were idiopathic, 2 (18%) had known history of trauma, and 1 (10%) had history of prior radiation. Anecdotally, it has been our clinical experience that the very proximal bulb as it extends into the membranous urethra is often spared in LS USD. In addition, the proximal bulbar and posterior (membranous/prostatic) urethra in males is homologous to the female urethra which is also largely spared from LS changes, despite the fact that LS is more common in females^{23, 24}. The apparent protective effect of this area of urethral epithelium will require confirmation and further study, but is provocative, perhaps implicating a congenital versus acquired disease process for idiopathic strictures of this area²⁵.

Despite the significant heterogeneity of the strictures seen in this study, the presence of inflammation did not affect pre-operative urinary symptoms or urethroplasty success rates. Importantly, our current treatments for USD do not consider inflammation, as this cannot as of yet be determined pre-operatively, and thus, we wouldn't expect outcomes to necessarily be different. Additionally, a large percentage of the repairs were excisional and thus, the overall recurrence rate of 11% was likely not large enough to detect a clinically meaningful difference.

There are limitations to the study that we will address here. This retrospective surgical series is biased towards shorter strictures amenable to excisional repair, as pathology was not routinely taken at our institution at the time of onlay urethroplasty – and though we believe

that analyzing the urethral tissue will help us understand stricture pathophysiology, it remains unclear if tissue biopsy at time of urethroplasty should become routine as the ability for pathology to direct post-operative or intraoperative care has not been established. Second, pathologic analysis was limited to the strictured urethra itself and did not include surrounding urethral mucosa. This limits our ability to determine if all pathologic tissue was excised and may have an impact on surgical outcome. Third, PROM data of importance relating to inflammation, including pain and overall health status, was only given routinely to patients at the end of the study period. Lastly, no standardized consensus criteria for the pathologic analysis of urethral strictures exist and in lieu of this, histologic criteria associated with LS were utilized which are also not standardized. Despite these limitations, what this study does confirm is that urethral strictures are much more heterogeneous, and complex, than has previously been reported. Recognizing this heterogeneity offers the potential for recognizing differences in disease pathophysiology, and potentially for etiology specific surgical treatments.

Conclusion:

Histopathologic analysis of urethral stricture specimens reveals significant tissue heterogeneity in otherwise clinically similar strictures. Chronic inflammation is commonly found in stricture specimens indicating active antigen presentation of unknown significance. Patients with inflammatory strictures report worse reported health. As USD is generally thought of as a static fibrotic process, this study suggests that many urethral strictures may be active and evolving, and that future treatments may need to consider this so to improve surgical and non-surgical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Histopathology and corresponding retrograde urethrogram of bulbar urethral strictures (white arrows) from four patients (A-D) displaying the spectrum of chronic inflammation observed in the study cohort. A) no inflammation with preservation of tissue architecture; B) mild inflammation (black arrow) with no epithelial infiltration by inflammatory cells; C) moderate inflammation with focal epithelial infiltration by inflammatory cells (black arrow); D) severe inflammation with mucosal ulceration (black arrow).

Table 1.

Patient characteristics, stricture characteristics, and stricture management of the study cohort

	n=100
Patient Characteristics	
Age, mean $\pm$ SD (years)	41.5 $\pm$ 16.3
Body mass index, mean $\pm$ SD (kg/m ²)	30.2 $\pm$ 7.19
Tobacco use, no.	39
Diabetes, no.	12
Presence of clinical lichen sclerosus, no.	4
Hypertension, no.	16
Hyperlipidemia, no.	17
HIV/AIDS history, no.	6
Coronary artery disease, no.	4
BPH, no.	1
COPD, no.	4
Peripheral vascular disease, no.	1
Stricture Characteristics and Management	
Stricture length, mean $\pm$ SD (cm)	2.60 $\pm$ 2.43
Stricture location, no.	
Penile	10
Bulbar	78
Bulbomembranous	11
Multifocal	1
Stricture etiology, no.	
Idiopathic	43
Iatrogenic	7
Traumatic	16
Failed hypospadias	4
Infectious	2
Lichen sclerosus	4
Radiation	2
Prior stricture management, no.	
DVIU	46
Urethral dilation	27
Urethroplasty	16
Repair type, no.	
EPA	66
Non-transecting EPA	15
Augmented anastomotic urethroplasty	13

	n=100
Other	6

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Table 2.

Identification of histopathologic features characteristic of lichen sclerosis, presence of inflammation, inflammation severity, and predominant inflammatory cell type on primary and re-review of surgical pathology

	Primary Review (n=100)	Re-review (n=100)	P
Specimens with histopathologic features characteristic of LS, no.			
Hyperkeratosis	14	36	0.0005
Thinning/thickening of epidermis	1	6	0.118
Degeneration of basal cell layer	0	0	-
Dermal collagen homogenization	1	8	0.035
Lichenoid lymphocytic infiltrate	25	38	0.067
Histopathologic features characteristic of LS identified, no.			0.0004
0	67	39	
1	27	40	
2	4	15	
3	2	6	
Inflammation present, no.		44	
Inflammation severity, no. (%)			
minimal		9 (20)	
mild		17 (39)	
moderate		17(39)	
Severe		1 (2)	
Predominant inflammatory cell type, no. (%)			
lymphocytes		38 (86)	
neutrophils		1 (2)	
macrophages		0	
plasma cells		5 (12)	
eosinophils		0	

Table 3.

Comparison of patient characteristics, stricture characteristics, prior management, urethroplasty technique, and surgical outcomes of patients with no inflammation, minimal to mild inflammation, and moderate to severe inflammation observed in the urethral stricture specimen

	Stricture Inflammatory Grade			
	None (n=56)	Minimal - Mild (n=26)	Moderate - Severe (n=18)	P
Patient Characteristics				
Age, mean $\pm$ SD (years)	40.1 $\pm$ 16.9	42.3 $\pm$ 15.7	44.7 $\pm$ 15.8	0.57
Body mass index, mean $\pm$ SD (kg/m ²)	29.9 $\pm$ 8.09	29.9 $\pm$ 5.71	31.5 $\pm$ 6.24	0.68
Tobacco use, no. (%)	19 (34)	12 (46)	8 (44)	0.5
Diabetes, no. (%)	3 (5.4)	5 (19)	4 (22)	0.07
Presence of clinical lichen sclerosus, no. (%)	0	1 (3.8)	3 (17)	0.007
Hypertension, no. (%)	12 (21)	9 (35)	5 (28)	0.44
Hyperlipidemia, no. (%)	7 (13)	7 (27)	3 (17)	0.27
HIV/AIDS history, no. (%)	1 (1.8)	4 (15)	1 (5.6)	0.05
Coronary artery disease, no. (%)	1 (1.8)	1 (3.8)	2 (11)	0.21
BPH, no. (%)	1 (1.8)	0	0	0.67
COPD, no. (%)	2 (3.6)	1 (3.8)	1 (5.6)	0.93
Peripheral vascular disease, no. (%)	0	1 (3.8)	0	0.24
Stricture Characteristics				
Stricture length, mean $\pm$ SD (cm)	2.63 $\pm$ 2.27	1.78 $\pm$ 1.1	3.62 $\pm$ 3.68	0.053
Stricture location, no. (%)				0.013
Penile	4 (7)	1 (3.8)	5 (28)	
Bulbar	42 (75)	23 (88)	13 (72)	
Bulbomembranous	10 (18)	1 (3.8)	0	
Multifocal	0	1 (3.8)	0	
Stricture etiology, no. (%)				0.49
Idiopathic	24 (43)	11 (42)	8 (44)	
Iatrogenic	4 (7.1)	1 (3.8)	2 (11)	
Traumatic	8 (14)	6 (23)	2 (11)	
Failed hypospadias	2 (3.6)	1 (3.8)	1 (5.6)	
Infectious	1 (1.8)	1 (3.8)	0	
Lichen sclerosis	0	1 (3.8)	3 (17)	
Radiation	1 (1.8)	1 (3.8)	0	
Management and Outcomes				
Prior stricture management, no. (%)				0.68
DVIU	27 (48)	11 (42)	8 (44)	
Urethral dilation	11 (20)	9 (34)	7 (39)	
Urethroplasty	9 (16)	4 (15)	3 (17)	

	Stricture Inflammatory Grade			
	None (n=56)	Minimal - Mild (n=26)	Moderate - Severe (n=18)	P
Repair type, no. (%)				0.33
EPA	38 (68)	18 (69)	10 (56)	
Non-transecting EPA	7 (13)	6 (23)	2 (11)	
Augmented anastomotic urethroplasty	7 (13)	1 (3.8)	5 (28)	
Other	4 (7.1)	1 (3.8)	1 (5.6)	
Post operative complications, no. (%)	3 (5.5)	1 (3.8)	0	0.6
Recurrent stricture, no. (%)				
Detected on cystoscopy	9 (16)	3 (12)	1 (5.6)	0.5
Requiring intervention	8 (14)	2 (7.7)	1 (5.6)	0.48
Follow up, mean $\pm$ SD (months)	26.8 $\pm$ 27	29.1 $\pm$ 19	17.3 $\pm$ 23	0.26

Table 4.

Patient reported outcome measures for inflammatory versus non-inflammatory strictures

Patient Reported Outcome Measure	Non-Inflammatory (n=20)	Inflammatory (n=17)	Overall (n=37)	p
Mean $\pm$ SD Urinary Symptoms (Range 0–4)				
Hesitancy:				
<i>Is there a delay before you start to urinate?</i>	2 $\pm$ 1.34	2.12 $\pm$ 1.17	2.05 $\pm$ 1.25	0.79
Strain:				
<i>Do you have to strain to continue urinating?</i>	1.85 $\pm$ 1.57	2.18 $\pm$ 1.47	2 $\pm$ 1.51	0.53
Interrupted urinary stream:				
<i>Do you start and stop more than once while you urinate</i>	1.95 $\pm$ 1.32	2.12 $\pm$ 1.11	2.03 $\pm$ 1.21	0.69
Incomplete emptying:				
<i>How often do you feel your bladder has not emptied properly after you have urinated?</i>	1.6 $\pm$ 1.32	2.18 $\pm$ 1.29	1.86 $\pm$ 1.32	0.19
Post-void dribbling:				
<i>How often have you had a slight wetting of you pants a few minutes after you have finished urinating and had dressed yourself?</i>	1.35 $\pm$ 1.23	1.53 $\pm$ 1.12	1.43 $\pm$ 1.17	0.65
Stream Strength:				
<i>Would you say that the strength of your urinary stream is...</i>	2.25 $\pm$ 1.65	2.67 $\pm$ 1.61	2.45 $\pm$ 1.62	0.35
Symptom interference (0–3):				
<i>Overall, how much do your urinary symptoms interfere with your life?</i>	1.55 $\pm$ 1.05	2.12 $\pm$ 0.928	1.81 $\pm$ 1.02	0.06
Evaluation of urinary flow
2.8 $\pm$ 1.01	3.25 $\pm$ 0.931	3 $\pm$ 0.986	0.23
Mean $\pm$ SD Health Status (Range 0–3)				
Mobility	1.15 $\pm$ 0.367	1.25 $\pm$ 0.447	1.19 $\pm$ 0.404	0.46
Self-care	1.1 $\pm$ 0.308	1.07 $\pm$ 0.258	1.09 $\pm$ 0.284	0.73
Usual activities	1.2 $\pm$ 0.410	1.13 $\pm$ 0.352	1.17 $\pm$ 0.382	0.60
Pain/discomfort	1.3 $\pm$ 0.470	1.53 $\pm$ 0.516	1.4 $\pm$ 0.497	0.16
Anxiety/depression	1.3 $\pm$ 0.571	1.53 $\pm$ 0.516	1.4 $\pm$ 0.553	0.20
Mean $\pm$ SD Overall Health				
We would like you to indicate on this scale how good or bad your health is today, in your opinion (range 0–100)	77.8 $\pm$ 16.5	67.2 $\pm$ 13.7	73 $\pm$ 16	0.04
How often do you have the following symptoms?, mean $\pm$ SD				

Patient Reported Outcome Measure	Non-Inflammatory (n=20)	Inflammatory (n=17)	Overall (n=37)	p
Leaking of urine because you cannot hold it (range 0–3)	1.15 ± 1.42	1.73 ± 1.28	1.4 ± 1.38	0.20
Pain in the bladder (range 0–3)	0.50 ± 0.867	1.07 ± 0.929	0.97 ± 1.34	0.06
Severity (range 0–10)	3.63 ± 3.46	3.93 ± 3	3.79 ± 3.13	0.93
Pain in the urethra/penis (range 0 – 3)	1.35 ± 1.32	0.875 ± 0.957	1.12 ± 1.17	0.23
Severity (range 0–10)	2.94 ± 2.81	3.63 ± 1.92	3.26 ± 2.39	0.41