

The Role of the Urinary Epithelium in the Pathogenesis of Interstitial Cystitis/Prostatitis/Urethritis

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The urothelium plays a pivotal role as a barrier between urine and its solutes and the underlying bladder. Bladder surface mucus is a critical component of this function. The biologic activity of mucus that imparts this barrier function is generated by the highly anionic polysaccharide components (eg, glycosaminoglycans), which are extremely hydrophilic and trap water at the outer layer of the umbrella cell. This trapped water forms a barrier at the critical interface between urine and the bladder. The result is a highly impermeable urothelium that serves as a key protective barrier for the bladder interstitium. In interstitial cystitis (IC), disruption of the urothelial barrier may initiate a cascade of events in the bladder, leading to symptoms and disease. Specifically, epithelial dysfunction leads to the migration of urinary solutes, in particular, potassium, that depolarize nerves and muscles and cause tissue injury. Exogenous heparinoids can restore the barrier function of the urothelium and thus successfully treat patients with IC. Groups of patients who have been given a diagnosis of IC, chronic prostatitis, and urethritis have been shown to have IC by virtue of their shared potassium sensitivity. It would seem, therefore, that mucous deficiency may be present throughout the lower urinary tract. If one is to rename these diseases, perhaps it is best to do so in reference to a shared loss of epithelial barrier function. A name such as lower urinary dysfunctional epithelium would incorporate all of these diseases under a single pathophysiologic process. As a result of these discoveries, a new paradigm for diagnosis and treatment is emerging. UROLOGY 69 (Suppl 4A): 9-16, 2007. © 2007 Elsevier inc.

Bladder surface mucus is composed of glycosaminoglycans (GAGs) and proteoglycans on the outer surface of the transitional cell apical membrane.^{1,4} Mucus, along with its contained solutes, provides the immediate interface between urine and bladder wall. As such, it represents the primary barrier in the bladder for controlling interactions with urine.⁵ Mucus may be critical in preventing a host of disease states such as infection, calculus formation, radiation cystitis, carcinogenesis, and interstitial cystitis (IC). Clearly, urine solutes were never meant to interact with the bladder during the storage phase of urine; mucus is important for this function.^{2,6} Consequently, it is imperative to understand the biologic mechanisms by which mucus exerts its activity to help explain how mucus works, what happens when it is defective, and most importantly, how its function can be restored.

Four major pieces of the puzzle have been identified to help explain the role of bladder mucus. The first major piece is that the mucus is a critical regulator of the

bladder's permeability to urinary cations and is dysfunctional in most patients with IC.

The second major piece is that potassium appears to play an important role in IC pathogenesis. Normally present in high levels in urine, potassium causes no symptoms in healthy individuals because the surface mucus protects the bladder against it. In individuals with IC, however, extensive evidence suggests that an epithelial permeability defect allows potassium to diffuse into bladder tissue and provoke symptoms. Most patients with symptoms of IC, chronic prostatitis, or chronic pelvic pain (CPP) who have been tested for intravesical potassium sensitivity tested positive, indicating that they have an abnormally permeable epithelium.

The third major piece of the puzzle is that heparinoid compounds (ie, heparin and pentosan polysulfate sodium [PPS]) repair experimentally induced injury of the bladder mucus. This finding has led to the development of drugs designed to repair mucosal dysfunction that are now being used in clinical practice for the successful management of IC.

The fourth major piece is the recent finding that normal urine contains a toxic factor capable of injuring the mucus, and that this cytotoxic effect is neutralized by the abundant urinary protein Tamm-Horsfall protein (THP). An abnormality in THP may in fact be the primary defect associated with IC that results in disease.

This review provides a comprehensive evidence-based

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examination of mucus and its activity. It explains how IC begins with defective bladder surface mucus that results in a dysfunctional epithelium and abnormally permeable membrane, and how these events, in combination with a cascade of subsequent events, eventually lead to disease.s

BLADDER MUCUS AND THE REGULATION OF EPITHELIAL PERMEABILITY

Bladder Mucus as an Antl adherence Factor

Some of the first evidence for bladder surface mucus as an important defense mechanism of the transitional epithelium came from investigations that explored the role of mucus in preventing urinary tract infections (UTIs). Several studies on the antibacterial defense mechanism of the bladder have shown that mucus serves an important role in preventing bacterial adherence.⁷⁻¹¹ When the mucus was removed with the use of solutions that contained acid or detergents, a marked rise in bacterial adherence and a resultant increase in bacterial infection were noted.⁷ Histochemical studies showed that bladder surface mucus removed by these treatments was resynthesized within 24 hours, and that the presence of mucus at the bladder surface coincided with resistance to bacterial adherence.⁷ These data support the hypothesis that bladder surface mucus plays a role in preventing UTIs.

Additional studies showed that not only can the mucus be removed, but exogenous substances can restore its antiadherence effect. Because bladder surface mucus is rich in GAGs,¹⁻⁴ heparin, an exogenous GAG, has been evaluated for its ability to exert an antiadherence effect. In experiments on bacterial adherence in rodent models (rabbits), an acid treatment was used to remove mucus, and heparin was then placed in the bladder for 15 minutes before exposure to bacteria. In one study, the antiadherence property of the bladder surface mucus increased and returned to near preinjury levels after heparin treatment.⁹ In a similar study, bacterial adherence in acid-treated bladders was 55-fold higher than in controls, whereas it was only 5-fold higher than in controls in bladders treated with heparin after injury.¹⁰

In addition, we hypothesized that mucus analogs (heparinoids) would act in a similar fashion to heparin. Thus, we examined PPS, a semisynthetic polysaccharide (a heparin analog), for its ability to restore the antiadherence activity of bladder mucus. These studies examined bacterial adherence, as well as the adherence of calcium and protein. All were found to be inhibited by intact bladder mucus or PPS administration after mucous injury.^{12,13} On the basis of these results, we hypothesized that bladder surface mucus not only prevents bacterial adherence but also acts as a universal antiadherence factor.

As would be found in later studies, PPS has an effect analogous to bladder surface mucus on the regulation of

epithelial permeability and is as effective as an oral drug. The use of heparinoid compounds in IC therapy is presented in even greater detail in an article by Moldwin *et al*.⁴

Role of Bladder Surface GAGs in Regulating Epithelial Permeability

Glycosaminoglycans are extremely hydrophilic. Sulfate moieties of the polysaccharide chains have marked avidity for water, making them infinitely soluble in a water-based solution.^{2,18-20} Engineers have taken advantage of these properties by using sulfated polysaccharides, such as heparin and polyvinyl sulfate, to coat industrial filters that prevent adherence, producing filters that last significantly longer than uncoated filters.²¹

We hypothesized a similar mechanism of action for GAGs on the surface of the bladder (Figure 1),²² with GAGs binding water to the surface of the transitional cell. This tightly bound water layer prevents the migration of urine solutes to the epithelial cell bilipid membrane and may very well serve as an antiadherent surface, preventing the interaction of urinary solutes with the epithelium.²³

Bladder surface mucus is another important protective mechanism of the bladder. Further, this critical interface between fluids in the lumen of the bladder (urine) and the cell membrane has a potential role in many diseases. It is hypothesized that infection, IC, calculus disease, radiation cystitis, chemical cystitis, and cancer may all share a common pathogenesis (ie, a dysfunctional bladder mucous lining).

This mucous hypothesis was tested by studying the effects on urothelial absorption of calcium and urea and binding of water at the bladder surface when mucus is replaced with PPS. The amount of calcium and urea absorbed from an intravesical solution before and after mucous injury by protamine sulfate was assessed with the use of in vivo rodent models (rabbits). To determine whether the absorption of calcium and urea was inhibited by the exogenously supplied sulfated polysaccharide PPS, PPS was administered after chemical injury of the mucus in 1 group of animals (Table 1 and Table 2).²⁰ As was hypothesized, epithelial absorption of urea and calcium did not rise significantly. In contrast, after mucous injury in a second group of animals that did not receive PPS treatment, epithelial absorption increased significantly for both calcium ($P = 0.007$) and urea ($P < 0.01$).²⁰

In this study, tritium-labeled water was also placed in the lumina of animal bladders and was allowed to equilibrate both before the mucosa was injured and after the injury had occurred and was reversed. Here, it was hypothesized that if mucus is hydrophilic and is thereby saturated with water (Figures 1 and 2),²² then when it is injured, the actual amount of water absorbed should decrease. Conversely, when the hydrophilic nature of the surface is restored, water should again bind and its volume increase. This was found to be the case.²⁰

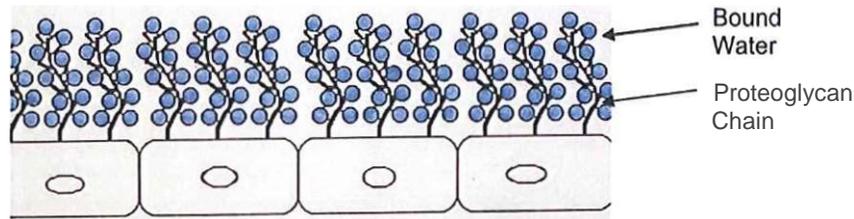


Figure 1. Glycosaminoglycans (GAGs) in the bladder surface mucus are hydrophilic and electrostatically bind to water. This drawing shows the water molecules bound to the epithelial cells, as represented by the shaded circles.

Table 1. Absorption of urea in rabbit bladders*

	Rabbit Bladder Treatment Group			
	Control	Protamine	PPS	Protamine + PPS
N	21	21	21	21
Average(%)	20.8	39.6	22.1	24.3
Urea absorbed (mg)	0.76	1.47	0.82	0.90
SD	5.7	6.9	4.9	5.2
Pvalue†			<0.01	<0.01

PPS = pentosan polysulfate.

*Data are expressed as percent movement of urea across the membrane. The percentages represent the radioactivity that was lost after the treatment was provided. Every bladder received a total of 3.7 mg of urea for each treatment.

†Compared with control group.

‡Compared with protamine.

Adapted with permission from J Urol.

Table 2. Absorption of calcium in rabbit bladders*

	Rabbit Bladder Treatment Group		
	Control	Protamine	Protamine + PPS
N	18	18	18
Movement of ⁴⁵ Ca mean,%	16.2	23.2	18.3
⁴⁵ Ca (mg)	0.065	0.09	0.073
SEM	5.8	11.5	8.0
Pvalue		0.007†	0.45

Tissue SEM

PPS = pentosan polysulfate.

*Protamines significantly raised ⁴⁵Ca movement. In addition, protamine significantly raised ⁴⁵Ca present in the mucosa, similar to results reported with urea.

†Compared with control.

‡Compared with protamine. PPS reversed protamine effect.

Adapted with permission from J Urol.

Figure 1 illustrates how the binding of water to the bladder surface is important in the function of mucus. Nickel and Comish⁴ found that if bladder surface mucus is fixed in the hydrated state with the use of an antibody to cross-link the backbone of the proteoglycans before it is prepared for electron microscopy, the areas represented by water are visible (Figure 2).²² The numerous spaces in the mucus represent bound water that is removed during the desiccation process in preparation for microscopy. When hydrated, this mucous layer can easily be as thick as a transitional cell.

Mucus as a Regulator of Solute Movement Across the Epithelium

It was further hypothesized that mucus regulates epithelial permeability because tightly bound water excludes urinary solutes. It was reasoned that this mechanism regulates the cation balance in the cell and keeps the sodium-potassium balance intact because the urinary lev-

els of these compounds are very different from the serum levels.

Another hypothesis was that mucus acts as a coarse tuning agent by excluding 80% to 90% of the solute from reaching the cell surface. It was theorized that the remaining 10% to 20% that does reach the cell surface is fine-tuned by the sodium-potassium pumps and water channels, and that these mechanisms work together to maintain critical intracellular and extracellular concentrations of both sodium and potassium.^{20,24}

To test this hypothesis, an experiment was conducted in rodents in which the solute urea was placed into the intact rodent bladder in vivo, was allowed to equilibrate, and then was measured after it had been absorbed. The mucus was then injured with protamine, after which a marked rise in urea movement occurred across the epithelium. After this injury, the use of PPS reversed this movement (Table 1).²⁰ The same experiment was conducted in normal human volunteers, in whom urea was placed in the bladder and its absorption measured. The

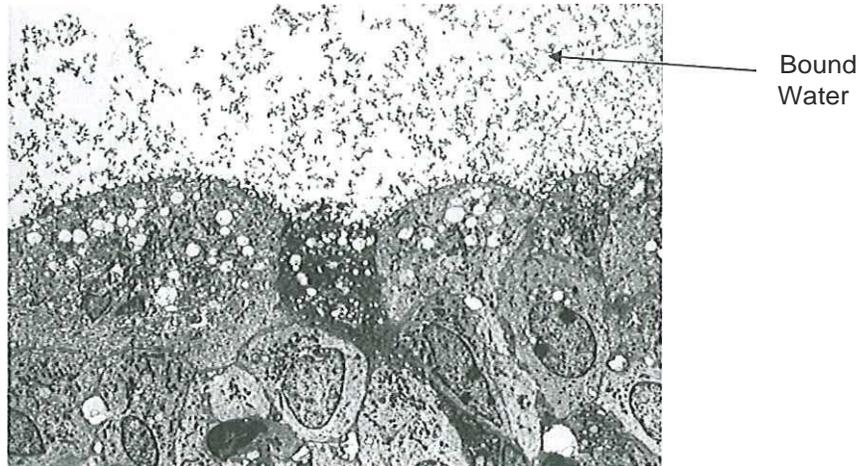


Figure 2. Transmission electron micrograph of the bladder mucosa shows the electron dense layer (bound water) covering the uroepithelium after the bladder surface layer was stabilized with specific antisera and ruthenium red. Original magnification: X2900. (Reprinted with permission from Urol Res.)²²

mucus was injured with protamine, after which a significant ($P < 0.02$) increase in the movement of urea occurred. Heparin was then used in an attempt to restore mucosal activity, and the movement of urea was again measured. As in the animal model, a marked decrease in urea movement was noted (Table 3).²³

To provide further evidence for the role of mucus in regulating epithelial permeability, isolated epithelial membranes of rabbit bladders were placed in Ussing chambers so the movement of solute across these membranes could be measured. Once the membranes had been equilibrated, the movement of ¹⁴C-urea was measured. The membrane was then injured with protamine, resulting in a significant ($P < 0.001$) 3-fold increase in urea movement. After injury, this increase could be reversed and urea movement decreased to control levels with a treatment of PPS.²⁰

In the studies just described, protamine sulfate was used to injure bladder mucus. Protamine sulfate was chosen as a more specific means by which GAGs in mucus could be injured, to further validate the critical role of GAGs in mucous activity. That is to say, if mucus is rich in heparin sulfate and chondroitin sulfate, it should be injured by the compound protamine sulfate. Protamine is known to have such a strong chemical attraction to heparinoids that it will form a salt with them and precipitate them from solution. As we reported, protamine injured the bladder mucus in a fashion similar to detergent and acid as a result of specific chemical interactions with the sulfated polysaccharides.²¹

Evidence for Abnormal Permeability Barrier in Patients with Interstitial Cystitis

These observations on the destruction and restoration of the epithelial permeability barrier gave rise to the hypothesis that individuals with IC have abnormal regulation of mucosal permeability. To test this hypothesis,

urea movement was measured in 31 normal subjects (Table 4)²⁵ and was found to average 4.3%. In patients with IC and no experimentally induced mucous injury, urea movement averaged 27%. In patients with Hunner ulcers, urea movement averaged 34.5%, which is both significantly ($P < 0.005$) greater than that for patients without Hunner ulcers (22.8%; $P = 0.002$) and consistent with the fact that patients with Hunner ulcers have worse symptoms and disease. These data provided strong support for the hypothesis that an abnormal mucous barrier on the epithelium of patients with IC leads to a marked increase in solute movement.²⁵

ROLE OF POTASSIUM IN PROVOCATION OF DISEASE

Potassium Sensitivity in Patients With IC

For the patient with IC who has abnormal epithelial permeability, the question arises as to whether a single solute or a number of solutes are relatively toxic to the bladder interstitium, which is composed of muscles and nerves. It has been hypothesized that potassium fulfills this role because its levels in urine are quite high, ranging from 24 to 133 mEq/L.²⁶ Such levels not only depolarize nerves and muscles,^{27,28} they may also cause tissue injury.

To test this hypothesis, normal subjects had a potassium solution placed in their bladders for 20 minutes, during which time a small amount of potassium was absorbed. After injury to the mucus with protamine, an increase in potassium absorption of approximately 7-fold was observed, which was reversed by heparin. Three of 19 (16%) subjects (Table 5) had some urgency associated with intravesical potassium before protamine treatment, but 15 of 19 (79%) subjects had a marked increase in urgency after protamine treatment, which was reversed by heparin.²⁹ It was concluded that, in normal subjects, movement of potassium across the epithelium was inhibited.

Table 3. Absorption of urea in the human bladder before and after treatment with protamine sulfate and heparin

Study Phase	Urea Movement (%)	Total Urea Movement (g)	B Value vs Control
Control	5.0	10.0	
Protamine	21.8	43.6	<0.02
Protamine followed by heparin	9.8	19.6	0.4

* Urea placed into each bladder totaled 200 g; therefore, the percentage represents a loss of 20 g, with 180 g remaining in the bladder after 45 minutes. Adapted with permission from Surg Gynecol Obstet.

Table 4. Absorption of urea in the human bladder of patients with interstitial cystitis (IC) versus controls

Group	N	Urea Absorbed (%)			P Value
		Mean	SEM	Range	
Controls	31	-4.3	±1.8	+33 to -34	
IC	40	-25.1	±6.5	+7 to -51	<0.005*

* Compared with controls using Student's t test. Adapted with permission from J Urol.

Table 5. Urinary symptom response to intravesical potassium in normal subjects before and after treatment with protamine and heparin

Stage	Subjects Reporting Symptoms, n (%)		P Value
	Urgency	Pain	
Baseline	3/19 (16)	0	
After protamine	15/19 (79)	7/19 (37)*	<0.001†
After heparin	8/19 (42)	2/19 (11)	0.04•

† Compared with baseline (Fisher exact test). • Compared with value after protamine (Fisher exact test). Adapted with permission from J Urol.

ited by an intact mucous layer. When the mucous layer was damaged by protamine, however, a significant increase in absorption ($P < 0.01$) and associated symptoms ($P < 0.001$) occurred, both of which were reversed by heparin.²⁹

This led to a test undertaken to compare intravesical potassium with sodium in a blinded fashion. In normal subjects, no reaction to sodium or potassium was reported before injury of the mucus with protamine. After the mucus had been injured with protamine, however, a marked increase in symptoms was seen in normal subjects who received potassium, with 90% reporting urgency. In contrast, only 10% of normal subjects had any reaction to sodium. After injury was reversed by heparin, a significant ($P = 0.035$) decrease in potassium sensitivity and no change in the already low level of sodium sensitivity were noted. These data clearly support the hypothesis that

potassium is the primary toxin responsible for generating the symptoms of IC.

On the basis of these data, a new potassium sensitivity test (PST) was designed for IC. Patients who met all National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria for IC,³⁰ as well as those who met the clinical criteria of the NIDDK (ie, did not have cystoscopy) were screened with a 5-minute potassium challenge versus a 5-minute water challenge to assess potassium sensitivity. After each instillation, patients rated their symptoms of pain, as well as urgency and frequency. The rate of potassium sensitivity was significantly higher ($P < 0.001$) in patients with IC than in controls, with approximately 75% of patients testing positive for potassium sensitivity compared with 4% of controls.²⁹ Because the sensitivity and specificity of this test are high, these results have been widely reproduced in centers around the world. The results of > 2500 PSTs performed in symptomatic individuals and controls have been reported. Cumulatively, these data indicate that potassium sensitivity was present in 1997 of 2555 (78%) patients with IC versus only 3 of 202 (1.5%) controls (Table 6).^{5,29,31-50} The PST, which was designed to be a scientific test of our potassium hypothesis, has turned out to be sensitive, specific, and valuable as a scientific and diagnostic tool.

Other Evidence Supporting Movement of Urinary Potassium Into the Bladder Interstitium

Additional support for potassium sensitivity as an indicator of epithelial dysfunction comes from a variety of sources. Using rodent models, Moss *et al.*⁵¹ showed that when the pelvic nerves are isolated, it is possible to selectively stimulate bladder innervation with potassium versus sodium. In another group, in which a rodent urodynamic model was used, it was shown that a marked increase in bladder hypersensitivity to potassium versus sodium occurs when the bladder epithelium is injured with protamine sulfate.⁵² In a study in which patients with IC were given sodium or potassium intravesically, urodynamic evaluations showed that patients had a marked reduction in bladder capacity after administration of potassium versus sodium.⁵³ Further support for the potassium hypothesis comes from a recent study that evaluated levels of urinary potassium in normal patients versus those in new untreated patients with IC. Data show that levels of potassium were significantly lower ($P = 0.001$) in patients with IC. This is consistent with the hypothesized movement of potassium into the bladder wall in patients with IC. Urine potassium levels in these studies ranged from 24 to 133 mEq/L [1 mEq/L = 1 mmol/L], and investigators determined whether these high levels of potassium would diffuse from the urine through defective mucus and into the bladder wall, where the potassium level is normally only 4 mEq/L. As expected, urine potassium levels in patients with IC who were successfully treated were significantly higher ($P = 0.025$) than in new untreated patients with IC.²⁶

Table 6. Reported results of testing for epithelial dysfunction in patients with lower urinary tract symptoms of frequency/urgency and/or pelvic pain versus controls

Study	N(%)	
	Patients	Controls
Parsons <i>et al.</i> (1994) ³¹	23/33(70)	1/22(5)
Payne and Browning (1996) ³²	18/20 (90)	
Parsons <i>et al.</i> (1998) ²⁹	174/231(75)	2/71(3)
Chambers <i>et al.</i> (1999) ³³	24/39 (62)	
Teichman and Nielsen-Omeis (1999) ³⁴	23/38 (61)	
Parsons <i>et al.</i> (2001) ³⁵	362/466(78)	0/42(0)
Chen <i>et al.</i> (2001) ³⁶	21/23 (91)	
Daha <i>et al.</i> (2001) ³⁷	12/13 (92)	
Forrest and Vo (2001) ³⁸	7/8 (88)	
Kuo (2001) ³⁹	40/40 (100)	
Gregoire <i>et al.</i> (2002) ⁴⁰	105/127 (82)	
Parsons <i>et al.</i> (2002) ⁴¹	302/377 (80)	
Parsons and Albo (2002) ⁴²	37/44 (84)	
Parsons <i>et al.</i> (2002) ⁴³	263/334(79)	0/6(0)
Parsons <i>et al.</i> (2002) ⁴⁴	197/244(81)	0/47(0)
Kuo (2003) ⁴⁵	138/196 (70)	
Parsons and Tatsis (2004) ⁴⁶	5/5 (100)	
Porrù <i>et al.</i> (2005) ⁴⁷	17/25 (68)	
Parsons <i>et al.</i> (2005) ⁴⁸	39/50(78)	0/14(0)
Chung <i>et al.</i> (2005) ⁴⁹	146/178 (82)	
Stanford <i>et al.</i> (2005) ⁵⁰	44/64 (69)	
Total	1997/2555 (78)	3/202 (1.5)

Adapted with permission from Urology.

A substantial body of evidence shows that the bladder epithelium has an important permeability regulatory mechanism in its surface mucus. Further, evidence indicates that when this surface mucus is intact and functioning, minimal urinary solute interchange with the bladder interstitium occurs, and that the epithelium and underlying bladder wall are protected. Data also show that IC is associated with significant epithelial dysfunction. Combined with the movement of potassium from the urine into the bladder interstitium, this dysfunction may lead to marked upregulation of neurologic activity, resulting in symptoms of urgency/frequency and pain and eventual tissue injury. This paradigm explains many of the clinical observations, as well as the majority of the experimental observations in patients with IC.

Potassium Sensitivity in the Urethra

Patients with IC/S and prostatitis⁴² have a high rate of disease-associated dysuria (58% and 77%, respectively). Dysuria is primarily a urethral symptom that likely reflects the fact that IC has a urethral component. To test the hypothesis that epithelial dysfunction in the urethra causes symptoms in the presence of potassium, we assessed, in a double-blind fashion, normal male volunteers (no IC symptoms) to determine their sensitivity to sodium versus potassium before and after protamine injury to the urethra. After urethral injury, significantly ($P = 0.008$) more subjects reported pain in response to potas-

Table 7. Potassium sensitivity in patients with active urinary tract infection (UTI) and in patients recovered from UTI

Status	Patients Tested (n)	Patients With Positive PST, n (%)
During acute UTI	4	4 (100)
Recovered from UTI	5	0

PST = Potassium Sensitivity Test
Adapted from Urol.

Table 8. Results of testing for epithelial dysfunction in symptomatic patients

Population	Patients Testing Positive for Epithelial Dysfunction, n (%)
IC	1285/1629 (79)
Urethral syndrome	64/116 (55)
CPP (gynecologic patients)	288/365 (79)
Category IIIA-III B prostatitis-CPPS	37/44 (84)
LUTS Men	83/526 (16)
Women	6/25(24)
Acute bacterial cystitis	4/4 (100)
Detrusor instability	4/16 (25)
Radiation cystitis	9/9 (100)

CPP = chronic pelvic pain; CPPS = CPP syndrome; IC = interstitial cystitis; LUTS = lower urinary tract symptoms.
Adapted from Urology.

sium than before injury, and significantly ($P < 0.001$) more subjects reported pain in response to potassium than to sodium chloride.⁴³

These findings led us to postulate that epithelial dysfunction may occur throughout the lower urinary tract, that is, in the bladder, prostate, and urethra.⁴³

Potassium Sensitivity in Other Populations: Lower Urinary Dysfunctional Epithelium

In keeping with the hypothesis that epithelial dysfunction occurs for a variety of reasons and is present in other known disease states, patients with symptoms from other causes were tested for potassium sensitivity. Patients with acute bacterial cystitis²⁹ and those with radiation cystitis³¹ had potassium sensitivity. After they recovered from infection, all patients returned to normal, with no potassium sensitivity noted (Table 7).²⁹

A search for epithelial dysfunction has been conducted in various patient populations, including women with a diagnosis of IC, urethral syndrome, or CPP, and men with a diagnosis of prostatitis or lower urinary tract symptoms (LUTS) (Table 8).⁵ Patients with IC and those with gynecologic pelvic pain have nearly identical rates of positive PST (78% and 81%, respectively).^{35,44} A lower but still substantial rate of positive PST (55%) occurs in the "urethral syndrome,"³⁵ lending support to our hypothesis that the urethral syndrome represents early-stage IC. In men with category IIIA or IIIB chronic

prostatitis/CPP syndrome (CPPS), 37 of 44 (84%) tested PST positive.^{4,2} In another study of male patients with a previous diagnosis of and antibiotic treatment for prostatitis, "50 of 50 (100%) patients had a score 7.7 on the Pelvic Pain and Urgency/Frequency (PUF) questionnaire scale, and 39 of 50 (78%) tested PST positive. In older men with LUTS, 83 of 526 (16%) tested PST positive."

Hence, if IC, urethritis, prostatitis, CPP, and male CPPS are to be renamed, perhaps it is best to do so by referring not to the symptoms, sex, or age of the affected patients but rather to the physiologic defect that may be operative (ie, epithelial dysfunction). Lower urinary dysfunctional epithelium (LUDE) may be a more appropriate term because it is all inclusive. A patient with dysuria has LUDE that involves the urethra; a patient with frequency/urgency has LUDE that involves the bladder and/or urethra. This nomenclature appears to be more accurate and provides a new paradigm that focuses on epithelial dysfunction, an underlying pathophysiologic process supported by considerable evidence.

POSSIBLE ROIE OF URINARY TAMM-HORSFAIIPROTEIN IN INTERSTITIAICYSTITIS

Data from recent investigations suggest that interactions between a urinary toxic factor (TF) and a protein macromolecule may play a major role in the pathophysiology of IC. Urinary TF has been documented in the urine of normal control subjects and in patients with IC.^{55,56} Urinary TF is cationic and hence is able to interact with the anionic bladder mucus, changing its ability to bind water to the bladder surface and thus impairing its permeability regulatory mechanism. Data indicate that THP, a highly anionic protein, has the capacity to neutralize the cytotoxic effects of TF, as does heparin.⁵⁵

These new findings suggest a model for the initiation of the mucosal dysfunction of IC. Such a model has been demonstrated by the known ability of protamine sulfate to cause mucosal injury in rodents and humans in a variety of studies, as was previously described. Protamine sulfate is a highly cationic substance that is capable of forming a salt with heparin. Similar compounds in urine that are also cationic may interact with the mucus in a similar fashion, impairing the normal regulation of permeability and starting the cascade of potassium cycling.

If THP exerts the neutralizing action suggested by these findings, this would explain its function in the urinary tract. Previously, there has been no explanation for why this highly conserved protein is present in large quantities in the urine of vertebrates.^{55,56} In the normal state, THP may act to scavenge and electrochemically bind cations that may cause mucous injury.⁵⁵ A defect in the glycosylated portion of THP that results in an abnormality of the protein's electrochemical activity could compromise a major protective mechanism in the lower

urinary tract, and permit the disease cascade of IC to begin.⁵⁶

CONCLUSION

Considerable evidence suggests that the disease called interstitial cystitis involves a urothelial permeability defect that allows urinary potassium to penetrate tissue and provoke symptoms. Studies show that this defect is present in most patients with IC who have been tested for it, as well as in many patients with symptoms of IC who have received a variety of other diagnoses. The emerging picture suggests a larger entity, LUDE, which encompasses the majority of cases that we have known as IC, chronic prostatitis, CPPS, and urethritis. Viewed as arising from a single pathophysiologic process that can be detected and addressed with tools currently available, these disorders can be recognized more readily and treated more effectively.

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