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The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain

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The traditional diagnosis of interstitial cystitis (IC) only recognizes the severe form of the disease. The far more common early and intermittent phases of the disease are not perceived to be part of IC but rather are misdiagnosed as urinary tract infection, urethral syndrome, overactive bladder, chronic prostatitis, urethritis, or a type of gynecologic pelvic pain (such as endometriosis, vulvodynia, or some type of vaginitis). All of these patient groups actually suffer from the same bladder disease. This disease results from a leaky bladder epithelium and subsequent potassium leakage into the bladder interstitium that generates the symptoms of frequency, urgency, pain or incontinence in any combination. Robust scientific data now support this important concept. These data will be reviewed herein. The conclusions derived from these data substantially alter the paradigms for urology and gynecology in the generation of frequency, urgency and pelvic pain. All the above-mentioned syndromes unite into one primary disease process, lower urinary dysfunction epithelium, or LUDE disease, and not the 10 plus syndromes traditionally recognized.

What's known on the subject? and What does the study add?
This article reviews entirely new concepts concerning the etiology, presentation and diagnosis of interstitial cystitis. It pulls the information together in a concise fashion that emphasizes there is a radical change taking place in the concepts of what generates bladder symptoms.

Primarily this emphasizes that the paradigm for interstitial cysititis and the generation of bladder symptoms is going to change dramatically. The data reviewed shows that the symptoms are caused by a leaky epithelium and subsequent diffusion of potassium into the tissues causing frequency, urgency, pain and incontinence. This is totally different from current concepts.

KEYWORDS

interstitial cystitis, urinary bladder, potassium

INTRODUCTION

Little was understood about interstitial cystitis (IC) in 1980. Only its existence and the severity of its symptoms were known. Reports on IC were present in the literature 150 years earlier, but nothing was understood concerning its aetiology and diagnosis was limited to one of exclusion in patients with severe bladder symptoms. In the 20th century Hunner's description of the elusive ulcer, Bumpus's description of petechial haemorrhages after bladder distension, and John Hand's excellent treatise on the clinical aspects of the disease summarized most of the knowledge of IC before 1975 [1]. The first modern development in the understanding of IC was when Messing popularized the concept of 'early IC', i.e. disease in younger people with less severe symptoms. This opened up the possibility of diagnosing the disease in patients years before they reached its late and severe phases [2].

This is common sense, since IC has to have a beginning and the initial phases of the disease would logically be milder and probably cause intermittent symptoms; yet the traditional diagnostic paradigm ignores these patients with early-phase disease (who represent the substantial majority). However, more modern approaches are currently being adopted. One unfortunate consequence of this narrow perspective of IC is that the clinician/researcher has been limited from developing new hypotheses based on the actual disease beginnings and instead has been channelled into focusing on patients with late-phase disease and all the secondary effects of the disease process.

Three decades of clinical, basic and translational research experience on thousands of IC patients at UC San Diego (UCSD) have resulted in a gradual evolution in my understanding of the pathophysiology of IC, its clinical presentation, diagnosis and therapy. The overall view is that the disease has an insidious development over many years from mild, intermittent symptoms to, in rare cases, classic severe IC. As the disease develops in patients, they are assigned diagnoses by clinicians based on the symptoms they are currently expressing, their

sex, and the specialist they consult. In this early phase, the diagnoses can include recurrent UTIs, overactive bladder (OAB), urethral syndrome, urethritis, prostatitis (in almost all cases in men), endometriosis, yeast vaginitis, vulvadynia or gynaecological chronic pelvic pain (CPP). Gynaecologists see many of the patients since women with IC have sexually associated symptom flares (and dyspareunia) and their menstrual cycle affects their IC symptoms [1,3,4]. As a result, a young woman whose urinary frequency is not perceived by her to be a problem is likely to self-refer to a gynaecologist, who will probably attribute her pelvic symptoms to a gynaecological source.

Working in partnership with my patients, my understanding of the disease has evolved and new discoveries regarding the aetiology of the disease have emerged. I have come to believe that there is probably only one primary disease process in the lower urinary tract that results in the generation of frequency, urgency pain and incontinence in patients <60 years old. After the age of 60 years, other factors in both men (obstruction) and women (e.g. UTI) are also involved in the generation of symptoms. While the disease runs its course in any one individual, different diagnoses might be ascribed to the cause of the symptoms, such as UTI, OAB, prostatitis or gynaecological CPP, but the generation of symptoms is probably originating from one problem in the urinary bladder: an epithelial dysfunction of the bladder mucosa that results in a loss of the normal permeability barrier, resulting in a 'leaky' epithelium. Coupled with the normally high concentrations of urinary potassium, this causes movement of potassium from urine to the bladder interstitium, which results in a cascade of reactions, causing symptoms, tissue injury and disease progression.

Contrary to historical belief, traditional IC actually represents only the severe and relatively rare form of this disease process and not a separate problem from the earlier phases of the disease.

Defining a disease by its symptoms rather than by its pathophysiology is often done in medicine when there is a lack of scientific evidence. The current push to rename IC 'painful bladder syndrome' is an example of this: the first symptom many patients experience is chronic frequency. Pain cycles develop later or not at all. There are several dangers with this arbitrary approach to classifying the disease. Patients are likely to be misdiagnosed and mistreated for perhaps years, and basic researchers who rely on their clinicians for input will be diverted into pathways that greatly restrict the development of new knowledge. A generic and more inclusive name like IC is preferable. Only as data emerge will modification of the name of the disease be justified. It would be sad to see efforts to rename the disease as part of a political rather than a scientific process.

This review will present evidenced-based information to substantiate the fact that lower urinary dysfunctional epithelium (LUDE) appears to be a principal cause of LUTS in men and women <60 years old.

THE PROTECTIVE ROLE OF THE MUCOSA AND THE MUCOUS LAYER

Transitional epithelium is a protective barrier for the bladder interstitium and functions to prevent urinary metabolites from interacting with the muscle layer and/or being reabsorbed and recycled back into the bloodstream, counteracting the function of the kidneys. Cell membranes and tight junctions are important components of the barrier and so is the surface mucus of the umbrella cells, also known as the glycosaminoglycan layer [5]. This mucus is highly anionic because of the sulphated polysaccharides on the glycosaminoglycan molecules and the sialic acid present in the glycoproteins. As a result, water is bound by electrostatic attraction to the mucus [6–9] and forms an 'unstirred water layer' [10,11] that blocks the movement of small molecules down to the cell surface. Research studies have confirmed that the epithelial mucous layer is critical in regulating the permeability of urinary solutes into the bladder wall [5,12].

In both *in vitro* and *in vivo* models, including rodents and humans, when the mucous layer of the bladder is chemically injured, there is a marked increase in solute movement across the epithelium, including water, urea, calcium and potassium [5,12–14]. In normal human subjects, the solutes that were examined were urea and potassium [5,12–14]. These acute injuries were reversed with heparin and pentosanpolysulphate, raising the possibility that these compounds could be used for therapy in people with a defective mucous layer.

Patients with interstitial cystitis have an abnormal, leaky epithelium as measured by urea, potassium, fluorescein and rhamnose movement across the transitional cell layer compared with normal asymptomatic controls [13–16]. We believe this 'leaky' epithelial dysfunction is probably the event that initiates the IC cascade of nerve up-regulation, muscle reactions and tissue injury.

THE ROLE OF URINARY POTASSIUM IN THE GENERATION OF BLADDER SYMPTOMS

The bladder epithelium is an important barrier that protects the underlying nerves and muscle from toxic urinary solutes. If the mucus is abnormal and the epithelium becomes permeable then urinary metabolites could diffuse into the muscle layer, provoking the symptoms of frequency, urgency, pain, incontinence and tissue injury.

One solute in particular, potassium, has the potential of causing serious reactions. At concentrations >8 mEq/L, potassium will depolarize nerves and muscles, and if the depolarization is prolonged, the cells will die [17]. Potassium concentrations in urine range from 30 to 120 mEq/L, with a mean concentration of 63 mEq/L [13]. Such high concentrations would readily diffuse down the gradient into the bladder wall and cause reactions.

To test the hypothesis that potassium was a key factor in generating bladder symptoms in IC, the potassium sensitivity test (PST) was developed [18]. The PST briefly exposes patients to water and then a potassium solution, and if they selectively responded to the potassium with a reaction of at least 2 (on a six-point scale) they were called positive. Patients with IC were tested and compared with asymptomatic control subjects. To date, the international literature contains over 35 published reports on potassium testing in over 3000 patients with IC/painful bladder syndrome (PBS) and the data are very robust, with 80% of patients with IC testing positive [19–25]. Furthermore, several reports included data on about 200 normal subjects and the test was negative in 98.3% [14,18,26,27].

Additional support for the hypothesis that potassium is involved in the generation of symptoms comes from experimental data collected in asymptomatic people. These

human subjects were catheterized and exposed to both sodium and potassium injected directly into their bladders and they did not react to either cation. These same volunteers had their bladder mucus injured by instillation of protamine sulphate, and after this treatment they reacted to potassium with symptoms, but not to sodium. Heparin placed into the bladder reversed the mucus injury and decreased the symptoms from a third exposure to potassium [14]. When the bladder mucus is experimentally injured, the potassium absorption into the bladder wall increases at the same time that symptoms are generated, and the absorption also decreases (as do symptoms) after the reversal of the injury with heparin [14].

What would happen to patients' potassium sensitivity if they were successfully treated and experienced symptom reduction? Logically, it should improve and, if so, it would further corroborate the role of potassium in the causation of bladder symptoms. To help answer this question, the PST was performed on patients before and after pentosanpolysulphate therapy in a large multicentre trial in North America that evaluated the effect of different doses of drug [27]. Patients who did not improve and who had a follow-up PST had no significant change in the PST results, while patients who did improve on treatment had a significant drop in their potassium sensitivity (Table 1).

There is yet another line of experimental evidence that supports the potassium hypothesis. If patients have a 'leaky' bladder epithelium and potassium absorbs into the bladder wall then the amount of potassium in their urine would be expected to be lower in IC patients with active symptoms. To test this concept, concentrations of potassium in the urine, normalized to creatinine, were measured in symptomatic IC patients and compared with normal subjects [13]. There was a significantly lower potassium concentration in patients (0.51 mEq/mg creatinine) than in control subjects (0.88 mEq/mg creatinine; $P < 0.001$). After treatment that improved symptoms, the potassium concentrations rose significantly to 0.66 mEq/mg creatinine ($P = 0.025$). If there is substantial reabsorption of potassium back into the bloodstream then the serum concentrations of potassium might be expected to rise, but this does not occur. The reason is that the large bowel secretes as much potassium in 24 h as do the kidneys, and the bowel will readily compensate for any transient elevations of potassium [28]. This is the basis for using enemas to quickly reduce serum potassium concentrations in renal failure.

POTASSIUM AND THE URETHRA

During micturition, the urethra is exposed to high urinary concentrations of potassium and could potentially suffer the same fate as the bladder if its protective mucous layer became dysfunctional. Most patients with IC, both men and women, report dysuria [3], and quite likely that potassium is the cause of this symptom. This could also explain dysuria in other diseases, such as bacterial urethritis or non-specific urethritis.

To determine if potassium could cause urethral discomfort, 22 normal male volunteers were recruited for a double-blind study. One-half of the subjects had their urethras exposed to a 0.4 M solution of potassium and the other half were exposed to sodium via irrigation with a small catheter; none experienced discomfort to either cation. They next had their urethras irrigated with protamine sulphate to chemically injure the urethral mucus. A subsequent irrigation with sodium caused no symptoms, but potassium resulted in burning discomfort in 90% of the volunteers [29]. Since most patients with IC have both bladder and urethral discomfort, it appears that epithelial dysfunction occurs in both locations. When the permeability barrier is abnormal, potassium effects on the tissues generate symptoms.

The potassium hypothesis explains all the symptoms experienced by the IC patients and converts IC from a syndrome into a disease, LUDE.

POTASSIUM SENSITIVITY IN SYMPTOMATIC PATIENT POPULATIONS

As a scientific tool, the PST has provided a means to test other symptomatic populations for potassium sensitivity, to determine whether epithelial dysfunction is causing the symptoms. Traditionally, many lower urinary tract conditions have been diagnosed on the basis of patient descriptions of symptoms and severity rather than objective, scientific evidence. Consequently, IC has been arbitrarily distinguished from other disorders, such as OAB, only by the presence of pain [30].

TABLE 1 Patients not improved vs those who were improved were compared at entry to the study and at exit. Improved patients had a significant drop in their pain responses to the potassium challenge compared with patients whose symptoms did not change

Patient group	*n*	Entry pain	Exit pain	*P*
Not improved	68	3.1	2.7	>0.2
Improved	85	3.2	1.3	<0.001

Minaglia *et al.* [31] performed the PST on over 100 patients with OAB and found 71% to be positive. A clever modification of testing for potassium sensitivity was reported by Daha *et al.* that employed a urodynamic model [19,32]. In brief, patients first underwent urodynamic testing with saline and then it was repeated with a potassium solution. Compared with the saline, potassium caused a mean reduction in bladder capacity (felt to be due to potassium causing a spasm of the muscle) of 15–23% in all patients with IC/PBS tested.

Subsequently, other investigators reported the same findings and it did not make any difference if the potassium infusion was given before or after the sodium. The results were the same; all patients with IC had reduced bladder capacities when exposed to potassium [20]. These same researchers tested both patients with OAB and those with IC and the potassium reactions were all positive in both groups [20,23]. In their discussion they felt the potassium might be directly affecting the muscle of the bladder, causing the reduced capacity they observed, and was probably due to an epithelial leak of the potassium. In addition, they raised the possibility that their results suggested that OAB and IC might not be separate diseases. These urodynamic data are in agreement with Minaglia *et al.*'s PST findings and the combination of both their results suggests it is reasonable to consider that patients with IC or OAB have one pathological mechanism – epithelial dysfunction – and a potassium leak that provokes tissue reactions. Furthermore, the fact that >80% of the patients with IC and OAB are women is certainly compatible with these two clinical entities being one disease.

Another major source of confusion leading to misdiagnosis of IC is that pain generated by a visceral organ such as the bladder does not

TABLE 2 Potassium sensitivity by clinical (gynaecologist) diagnosis

Clinical diagnosis	*n*	PST-positive, *n* (%)
Pelvic pain	93	71 (76)
VV	45	37 (82)
Dyspareunia	28	25 (89)
UFS	24	18 (75)
Endometriosis	22	19 (86)
UTI (recurrent)	15	12 (80)
Other	31	11 (85)
IC	4	4 (100)
Total	**244**	**197 (81)**

localize well. In my experience with thousands of patients, it can refer to any location, from the navel to the knees. It can be perceived solely in the left lower quadrant or as diffuse lower abdominal pain or in the labia, scrotum, perineum, vaginally peri-rectal, low back or in the medial aspect of the thighs [3,26]. Most patients I have seen do not fit the classic 'pain is worse with filling and relieved by emptying the bladder'. Many patients sense more of a chronic pain, burning, discomfort or pressure in the pelvis, lower back or thighs not perceived to be from the bladder.

Yet others experience the pain only during and/or after the act of voiding and might delay urinating to prevent it [26]. This voiding flare is readily explained by increased potassium leak due to the combination of osmotic and increased hydrostatic pressure associated with micturition. It is this referral of bladder pain that is responsible for most of the confusion and misdiagnoses made by urologists and gynaecologists. The fact is that urological patients with IC and gynaecological patients with CCP have the same symptoms: frequency, urgency, pelvic pain, menstrually associated symptom flares, dyspareunia and sexually associated flares (same for the men). However, a urologist or gynaecologist will routinely assign a diagnosis to the same patient based solely on their specialities, e.g. IC, recurrent urinary infection, endometriosis, vulvadynia or yeast vaginitis.

The patient herself is in large part responsible for these diagnostic problems. Women being followed by gynaecologists for CPP often do not perceive their bladders to be the source of their difficulties, especially as their pelvic pain is affected by their menstrual cycle and will usually have dyspareunia or a flare of their symptoms after sexual activity. Thus to the patient it does appear to be a gynaecological issue. As a result, she will self-direct to her gynaecologist for what she believes to be a gynaecological problem. The gynaecologist is unlikely to notice the presence of urological symptoms, primarily frequency of urination, as the patient will not report it. She may think voiding 12–14 times a day is normal (it is for her), so when asked if she has a problem, she will say no. As a result the women who have pain flares associated with the menstrual cycle will be told they have endometriosis, while if the pain is in the labia they will be diagnosed with vulvadynia, and if it is vaginal they will be diagnosed with vaginitis.

The confusion continues to build when one considers the issue of endometriosis. It is well established in gynaecology that patients with minimal or no endometriosis can be associated with severe pelvic pain, while many with severe endometriosis have no symptoms. I say 'associated pain' because it has never been scientifically proven that endometriosis causes any pelvic pain; it is more or less a convention to simply ascribe pain to pelvic findings such as adhesions or endometriosis without proof. In my practice, I have seen many patients who have had hysterectomies for pelvic pain but who did not experience relief.

Also, many of my patients have had diagnoses of vulvadynia, pelvic adhesions and yeast vaginitis from symptoms that were ultimately shown to be from their bladders. This led me to recruit four gynaecologists to determine with what frequency (if any) the bladder was generating the pain in their pelvic pain population. The studies included screening the patient for IC symptoms with the Pelvic Pain, Urgency, and Frequency Questionnaire (PUF) [26], performing a history and physical examination, conducting a PST and assigning a clinical diagnosis using their traditional criteria. The results were both surprising and very interesting: about 81% of the patients had positive PSTs and 85% had urological symptoms [17,33]. No matter what clinical diagnosis (Table 2) the patient was given – CPP, endometriosis, vulvadynia, yeast vaginitis – all had the same percentage (80%) of positive PSTs. These data imply that the patients with urological IC and those with gynaecological pelvic pain have the same disease. This is a dramatic paradigm shift for gynaecology, where IC goes from a rare diagnosis to the most common cause of CPP.

Other gynaecologists have reported additional studies with similarly high rates of positive PST results (≥80%) for patients with CPP [34–36]. In a large study of more than 100 patients with vulvadynia, >80% had a positive PST [37], and in another report 83% of patients (n = 40) were PST-positive [36]. These two studies highlight the fact that bladder pain can refer solely to the labia so that is not perceived to be from the bladder nor is the pain affected by bladder filling and emptying.

The conclusions from these studies are quite dramatic. The data show that epithelial dysfunction and potassium leak cause most of the pelvic pain in the gynaecological population; this is a drastic shift in the paradigm. The PST proved to be a valuable scientific tool since it was able to provide evidence that the bladder was the principal pain generator for gynaecological CPP. These results also underscore the fact that bladder pain refers anywhere in the pelvis, perineum, low back, vagina, scrotum, labia or thighs and is usually not perceived to be from the bladder. This is a critical point and is in contradistinction to what many urologists still believe, namely that the only pain seen in IC is obvious bladder pain 'made worse with bladder filling and relieved by emptying'. It is critical to integrate this new knowledge into our paradigm, if IC is to be diagnosed properly, and if we are to continue discovering the causes of this disease.

The male patient with IC raises another interesting issue. Almost all men (<50 years of age) when initially presenting with symptoms of frequency, urgency and/or pelvic pain will be diagnosed by almost every primary care physician and urologist as having prostatitis or CPP syndrome. But men with IC have similar symptoms to women with IC, including voiding symptoms, sexually associated symptom flares and the presence of pain anywhere from the navel area to the thighs, suggesting that perhaps they are one and the same disease [26,38,39].

To test this possibility, men clinically diagnosed with prostatitis were subjected to the PST. In all, 84% were positive for potassium. In a subsequent study in 50 patients with prostatitis, 77% were potassium-positive compared with 0% in 14 asymptomatic controls [29]. An additional study reported 84% positive PSTs in 31 patients [22]. There was a report that

mistakenly performed the PST using a 100 mL volume of fluid instead of 40 mL. The control subjects had an approximately 38% symptom response to plain water from volume sensitivity and so no conclusions can be drawn from their findings [40]. The PST provides scientific evidence that prostatitis and IC could be on a continuum of the same disease process: epithelial dysfunction and potassium leak, or LUDE.

Patients with urethral syndrome, who are primarily women, experience flares of frequency, urgency and/or pelvic pain and dysuria in the absence of a bacterial infection. My experience with these patients led me to consider the fact that they were 'early IC' [2], when the symptoms are less severe and intermittent. To explore this I selected patients with classic urethral syndrome, defined as having acute symptom flares for no more than 3 months and negative urine cultures [3]. When compared with patients with IC, they were younger and had a lower rate of positive PST (55 vs 78%), but they had the same symptoms and identical locations of pain throughout the pelvis. The potassium reactions in the patients with urethral syndrome were significantly less intense than in patients with IC, as would be expected. The PST findings in both IC and urethral syndrome confirm that they both have epithelial dysfunction, but the patients with urethral syndrome have milder intermittent disease and probably represent 'early IC'.

In summary, the PST results in symptomatic patient populations, including OAB, IC, gynaecological CPP, prostatitis and urethral syndrome, provide scientific evidence that all these populations probably suffer from one primary pathological process – lower dysfunctional epithelium – that results in a potassium leak into the bladder wall that provokes tissue reactions.

CONCLUSION

As a result of the accumulation of data over 30 years, my understanding of IC/PBS has evolved into an entirely new model. I now believe that there is one primary disease process that is responsible for the generation of LUTS consisting of frequency, urgency, pain and incontinence in men and women <60 years of age. This process is a leaky dysfunctional epithelium combined with potassium diffusion into the bladder wall that causes depolarization of sensory nerves and muscles and injures tissue.

This concept is now supported by very robust data that have been widely published in the international literature. IC/PBS, OAB, gynaecological CPP, prostatitis, CPPS and urethral syndrome have all been shown to have epithelial leak and potassium sensitivity, uniting these syndromes into one disease, LUDE.

Classic IC is not a different disease; it is just the severe and rare form of LUDE. The historic method of separating these syndromes arbitrarily according to the different symptoms the patient might express can now be replaced by evidence-based medicine that relies on the actual pathophysiology of the problem to define the disease. This represents a dramatic change in the traditional paradigm for the generation of bladder symptoms and opens new vistas for scientific discovery.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **CPP**, chronic pelvic pain; **IC**, interstitial cystitis; **LUDE**, lower urinary dysfunctional epithelium; **OAB**, overactive bladder; **PBS**, painful bladder syndrome; **PST**, potassium sensitivity test.