



The Association between Chronic Inflammation and Recurrent Cystitis in Women

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Recurrent urinary tract infection is a common infectious disease seen in the clinic. It is very prevalent in women; as many as 15% of women develop urinary tract infection each year, and at least 25% have one or more recurrences. Chronic inflammation and increased urothelial apoptosis reflect a common pathophysiology in various lower urinary tract dysfunctions, causing bladder storage symptoms. It has been suggested that chronic inflammation could be associated with overactive detrusor and increased levels of urinary nerve growth factor and creatinine. The level of urinary nerve growth factor may decrease after an effective antimuscarinic therapy. Recurrent urinary tract infection could be prevented by using nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors. Intravesical hyaluronate and chondroitin sulfate reduce the incidence of recurrent bacterial cystitis, and treatment with hyaluronate targets bacterial adherence to the bladder mucosa in interstitial cystitis/bladder pain syndrome. This article reviews the pathophysiology of chronic inflammation of the bladder and investigates the association between chronic inflammation and recurrent urinary tract infection.

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INTRODUCTION

Inflammation of the bladder can be due to both non-infectious and infectious etiologies. The most common cause of infectious cystitis has been *Escherichia coli* in Korea [1]. Noninfectious cystitis can be due to a variety of causes, including medication, radiation, foreign bodies, chemicals, and autoimmune responses, and can even be idiopathic [2]. Inflammation of the bladder wall has a direct effect on the function of the bladder. Indeed, chronic inflammation of the bladder wall may not be caused by bacteria and may not respond to conventional antibiotic therapy. The inflammation stiffens the bladder wall, making it difficult for the bladder to fully expand when holding urine [3].

In both human and animal models, chronic inflammation of the bladder is closely associated with the characteristics of overactive bladder (OAB) and overactive detrusor [4,5]. It can affect both women and men, although it is more common in women. This chronic inflammation has also been called bladder pain syndrome (bladder pain syndrome, BPS), and has been commonly known as interstitial cystitis (IC). However, the cause is unclear.

Recurrent urinary tract infection (UTI) is a common infectious disease seen in the clinic, and is very prevalent in women [6]. More than 50% of women have at least one episode of UTI during their lifetime [7]. As many as 15% of women develop UTI each year, and at least 25% of them have one or more recurrences [8,9]. A recurrent

UTI negatively affects patient's quality of life, significantly contributing to the extremely high financial burden of UTI, which, through direct medical costs and indirect costs, such as lost work output, is estimated to be more than US\$5 billion in the United States alone [10-12]. Moreover, urothelial damage and chronic inflammation results from UTI. It has been suggested that chronic inflammation could be associated with overactive detrusor and increased levels of urinary nerve growth factor (NGF) and creatinine. Indeed, many patients with recurrent UTIs may have bladder oversensitivity without infection [13]. Although this may seem likely to be a neurogenic problem, the underlying causes of these conditions in women are not clear. Herein, we review the pathophysiology of chronic inflammation of the bladder and investigate the association between chronic inflammation and recurrent UTI.

CHRONIC INFLAMMATION AND DETRUSOR OVERACTIVITY (OVERACTIVE BLADDER)

Acute inflammation is the first response to any noxious stimulus or injury. It is characterized by increased vascular permeability, leukocyte migration to the site of injury, and activation of a biochemical cascade of inflammation. Inflammatory activation is caused by a release of mediators, such as cytokines, kinins, histamines, nitric oxide, clotting factors, complement factors, and proteases [2]. In the case of acute cystitis, these mediators cause erythematous swelling and ulceration of the bladder mucosa, which bleeds easily. The surface layer is shed, forming small and clear cysts (sacs with liquid, gas, or semisolid contents) that are frequently seen on a cystoscopy. Moreover, these mediators cause bladder mucosal irritation, which is responsible for urgency, increased frequency, and dysuria. The systemic release of inflammatory mediators causes low-grade fever. In general, these mediators have a short half-life and are quickly degraded, enabling a rapid resolution of inflammation with the removal of noxious stimulus. However, with continuous stimulus, chronic inflammation of the bladder ensues.

Overactive detrusor and lower urinary tract dysfunction (LUTD) are associated with chronic inflammation of the bladder [3]. Birder and Andersson [14] suggested that the urothelium plays an important role in the modulation of

ending the excitability of the bladder sensory nerve. It is likely that chronic inflammation of the bladder might be the rudimentary cause of LUTD, and storage symptoms were associated with the increase of sensory receptors expression in the suburothelium and urothelium [15,16]. Although the underlying pathophysiology may differ, the urotheliums of LUTD patients have been observed in molecular mechanisms involving abnormal overexpression of sensory receptors and NGF [16]. An effective management of non-neurogenic OAB and neurogenically overactive detrusor is noted to decrease urinary NGF [15]. It means that LUTD could be related with the association between the increase of sensory receptor expression and bladder inflammation. Chronic inflammation of the bladder and abnormal urothelial changes could reflect the common pathophysiology of LUTD that cause storage symptoms [3].

IRREVERSIBLE DESTRUCTION OF THE BLADDER

The urothelium is a unique mucosal tissue in which the regulatory immune networks remain mostly unrevealed, and much research is still needed regarding this. The bladder also experiences a high incidence of recurrent infections, raising the question of where the balance lies for this organ with respect to the decision to evaluate and treat. With its specialized function and physiology of storing host waste products, it is essential for the bladder to balance the host defense and the need to limit any inappropriate responses to self-products, as well as to minimize tissue damage [17]. Although the underlying cause has not been fully elucidated thus far, the high incidence of recurrent UTI suggests a defect in the immunological memory formation subsequent to bladder infection. Many clinical reports indicate that cystitis, unlike pyelonephritis, fails to evoke detectable pathogen-specific antibodies in the serum and urine [18,19]. However, Chan et al. [17] had identified a broadly immunosuppressive transcriptional program specific to the bladder, but not to the kidney, during a UTI, which was dependent on tissue-resident mast cells (MC). This involves localized production of interleukin (IL)-10 and results in suppressed humoral and cell-mediated responses and bacterial persistence. Indeed, these MC activities in the bladder wall reflect not only the severity of inflammation but also the bladder symptom presentation in LUTD.

Without referencing the etiology, it has been known that extended duration of noxious stimulus results in chronic inflammation. This is characterized by the infiltration of mononuclear cells, such as MC, macrophages, eosinophils, plasma cells, and lymphocytes. The infiltration of mononuclear cells leads to inevitable destruction and dysfunction of the urothelium, such as fibrotic changes, decreased bladder compliance, and overactive detrusor. Hyperalgesia and LUTD are caused by these structural and functional changes in the bladder. As a result, a cascade of interrelated events is initiated, resulting in a vicious, self-reinforcing cycle of persistent inflammation and recurrent injury to the bladder epithelium [20].

CHRONIC INFLAMMATION AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Arya et al. [13] suggested that women with recurrent UTI, compared with control subjects, were correlated more with urinary frequency and increased bladder sensation in the absence of active infection. Their findings suggested that women with recurrent UTI should endure evaluation and treatment of episodes of infection to prevent the development of oversensitive detrusor. Other studies showed that positive urine culture at 10^5 CFU/ml in women is significantly associated with lower urinary tract symptoms, such as nocturia, urgency, urgency incontinence, and nocturnal enuresis [21,22]. Additionally, bacteriuria is also associated with bladder pain. These support an aspect for bacterial infection in the pathogenesis of non-neurogenic OAB and neurogenic detrusor overactivity [23].

Severe pyuria and bladder inflammation with elevated serum IL-5 and serum and urine IL-6, the neutrophil chemokine CXCL1, and granulocyte colony-stimulating factor are predictive of chronic infection [24]. This chronic bladder inflammation manifests as both lymphonodular hyperplasia in the bladder submucosa and urothelial hyperplasia, with a lack of uroplakin expression, which is a marker for terminal differentiation, in the superficial facet cells [25]. Similar histological findings have been observed in humans with persistent bacteriuria and recurrent UTI [26]. In a rodent model of OAB, Jang et al. [27] demonstrated that intravesical cyclooxygenase (COX)-2 inhibitors can alter the expression of inflammatory

modulators and cytokines in the bladder tissues improving the parameters of detrusor contraction. In mice, Hannan et al. [24] found that the inhibition of COX-2 reduced pyuria and prevented mucosal damage, but did not disrupt any known beneficial mucosal responses, such as urothelial exfoliation and overall immune cell recruitment to the bladder. Moreover, these findings suggested that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors provided positive outcomes as the treatment and prevention of UTI in susceptible patients. Although larger clinical trials are needed, chronic inflammation of the bladder was correlated with detrusor contraction, and recurrent UTI could be prevented after the use of NSAIDs or COX-2 inhibitors.

URINARY NERVE GROWTH FACTOR AND URINARY TRACT INFECTION

Several urological diseases, including bacterial cystitis, urinary stone, OAB, and IC/BPS, may develop storage symptoms. Lower urinary tract symptoms, including storage symptoms, seem to be caused by increased endogenous NGF. NGF has been suspected as a chemical mediator of pathology-induced changes in C-fiber afferent nerve excitability and reflex detrusor activity [28,29]. Recent studies showed that OAB and IC/BPS patients have been detected by increased urinary NGF levels compared with control patients [30,31]. For example, OAB-wet could be an inflammatory disorder, and urinary NGF could be a biomarker for bladder inflammation in OAB-wet [32,33]. OAB-wet and OAB-dry patients have significantly increased urinary NGF levels compared with control women and patient with increased bladder sensation [32]. Indeed, any urinary tract diseases that can cause lower urinary tract inflammation can increase urinary NGF production [34].

In cystitis patients, 36.7% (11/30) had OAB symptoms after 7 days of antibiotic therapy [34]. While 19 patients without OAB symptoms after the treatment showed a significant decrease in the levels of urinary NGF and creatinine, patients with OAB symptoms after the treatment did not show such a change. These urinary NGF levels decrease after an effective antimuscarinic therapy, but remain elevated 12 months after the treatment in patients with OAB symptoms, suggesting that residual inflammation might be present in the bladder wall. If inflammation has

been continuous, then OAB symptoms also persist. Bladder inflammation could be related to overactive detrusor, and increased levels of urinary NGF creatinine suggested that chronic inflammation is involved.

RECURRENT CYSTITIS AND GLYCOSAMINOGLYCAN

Uropathogenic *E. coli* (UPEC) causes approximately 85% of community-acquired UTIs, and virulent multi-drug resistant UPEC clones have recently emerged worldwide [35]. Women aged 55 years and older have a 53% chance of experiencing recurrent UTI, and UPEC is implicated in approximately 78% of recurrences [36]. There are two main outcomes of UPEC bladder infection in naive mice: i) sterilization of the urine within days of acute infection with or without the establishment of a quiescent intracellular reservoir [37,38], or ii) persistent high-titer bacteriuria and chronic high-titer bladder infection with chronic bladder inflammation that lasts for the lifetime of the animal if not cleared by appropriate antibiotics [25]. Glycosaminoglycan (GAG) is an important component of this protective lining and various coating techniques have been used to try and repair this layer with variable results. It has been postulated that a deficiency in the protective lining of the bladder epithelium is a common pathway in the development of IC/BPS, UTI, and bladder carcinoma [39-41]. For the protective effect, the luminal surface contains a greater concentration of sulfated (negatively charged) GAGs than the intracellular and interstitial locations [42]. When the surface GAG layer is damaged, urinary chemicals can “leak” into the surrounding tissues, causing pain, inflammation, and urinary symptoms. IC/BPS is an inflammatory disease of the bladder that can cause ulceration and bleeding of the bladder lining, which can lead to scarring and stiffening of the bladder.

In chronic inflammation of the bladder, the concept of a cyclical process is often proposed, with the idea that if one breaks the cycle of recurrence, it will lead to healing (Fig. 1) [2]. As such, treatment is directed at the urothelial layer, nervous system, and immune system in order to break the cycle of pain at various stages. Raymond et al. [43] studied 40 women who received intravesical hyaluronate (HA) once per week, for a duration of 4 weeks, and then once per month, for a duration of 4 months. There was

no recurrence during the 5-month treatment phase and 70% of patients were recurrence-free at the 1-year follow-up. In a randomized controlled study, intravesical HA and chondroitin sulfate (CS) in combination significantly reduced cystitis recurrence and improved urinary symptoms, quality of life, and cystometric capacity in recurrent bacterial cystitis patients at the 12-month follow-up versus antibiotic prophylaxis [44]. In another randomized placebo-controlled study [45], intravesical HA and CS also significantly reduced the cystitis recurrence rate without severe side effects. IC/BPS was correlated with chronic bladder inflammation and recurrent UTI. In contrast to antibiotic therapy, which aims at eradicating pathogens, treatment with HA targets bacterial adherence to the bladder mucosa under the presumptions that (1) a damaged GAG layer facilitates bacterial adherence and therefore recurrent UTI, and (2) the repaired GAG layer is capable of preventing adherence [45].

PREVENTION OF RECURRENT URINARY TRACT INFECTION

The ability of probiotic has long been considered to manage UTI. There is a close correlation between the loss of the normal genital microbiology (such as *Lactobacillus* species) and an increased incidence of UTI [46], suggesting that filling may be favorable [47]. A Cochrane review of cranberry products before 2007 concluded that cranberry products (drinks and capsules), significantly reduced the incidence of UTIs at 12 months compared with the placebo [48]. In 2015, another Cochrane review concluded that probiotics did not significantly reduce the prevention of UTI compared with the placebo or no treatment [49]. However, cranberry juice may decrease the number of

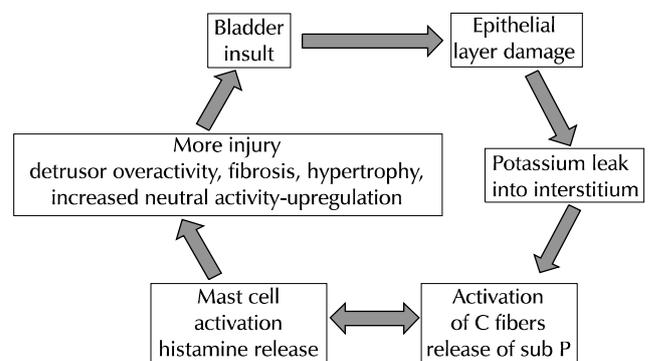


Fig. 1. The cycle of chronic bladder inflammation.

symptomatic UTI over a 12-month period in women with recurrent UTI [50]. Additionally, other studies showed that cranberry reduced the occurrence of UTI compared with the placebo in women with recurrent UTI [51,52]. Cranberry juice and products (tablets and capsules) have limited information on the effectiveness and serious adverse effect, but current evidence cannot rule out a reduction in recurrent UTI in women.

Uro-Vaxom[®] (Aju Pharmacy, Seoul, Korea) has been known as an *E. coli*-based oral vaccination against UTI. It could be used as a stimulant of dendritic cell maturation [53]. The efficacy of Uro-Vaxom[®] for the prophylaxis of recurrent UTI was tested in placebo-controlled, double-blinded studies [54-58]. In these trials, patients taking one Uro-Vaxom[®] capsule per day for 90 days experienced considerably less recurrent UTIs than patients taking placebo. These results showed that significant effects of Uro-Vaxom[®] on the incidence of UTI were observed during the 12-month study period and the safety profile was good and consistent. Although, more studies are needed to provide convincing evidence that probiotics and *E. coli* extract are equally effective as antibiotic prophylaxis for the prevention of recurrent cystitis.

CONCLUSIONS

Chronic bladder inflammation is associated with overactive detrusor and LUTD. These changes lead to inevitable destruction and dysfunction of the urothelium, such as fibrotic changes, decreased bladder compliance, and overactive detrusor. MC activities in chronic bladder inflammation reflect not only the severity of inflammation but also the bladder symptom presentation in LUTD. As a result, which are interrelated with each other is initiated, resulting in a vicious, self-reinforcing cycle of persistent inflammation and recurrent injury to the urothelium. IC/BPS was correlated with chronic bladder inflammation and recurrent UTI. The recurrent UTI rate was reduced with intravesical HA and CS without severe side effects. Longer follow-up and larger patient numbers will be required to confirm the relationship between chronic inflammation and recurrent cystitis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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