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ORIGINAL ARTICLE

Increased Chronic Urothelial Inflammation and its Association with Urinary Tract Infection

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ABSTRACT

Introduction: Inflammation of the bladder can be due to both noninfectious and infectious etiologies. The most common cause of infectious cystitis has been Escherichia coli.

Objectives: The basic aim of the study is to find the increased chronic urothelial inflammation and its association with urinary tract infection.

Material and methods: This cross sectional study was conducted in Ganga Ram hospital, Lahore during June 2020 to December 2020. The data was collected from 50 patients. Bladder symptoms and lower urinary tract conditions were investigated. All patients were treated actively according to the latest urine culture and followed by antimicrobial prophylaxis for at least 1 month.

Results: The data was collected from 50 patients. The mean age was 45± 3.56 years for male and 52.3 ± 8.89 years for females. The analysis of data shows the differences in urodynamic variables between the control subjects and the ESRD/CKD patients.

Conclusion: It is concluded from our study that increased urothelial inflammation and apoptosis and decreased cell expression were found in patients with ESRD/CKD.

INTRODUCTION

Inflammation of the bladder can be due to both noninfectious and infectious etiologies. The most common cause of infectious cystitis has been Escherichia coli [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 caused by bacteria and may not respond to conventional antibiotic therapy.

Recurrent urinary tract infection (UTI) is a very bothersome and a popular problem in the urogynecology clinical practice. According to the IUGA/ICS joint report on the terminology for female pelvic floor dysfunction, recurrent UTI is defined as at least three symptomatic and medically diagnosed UTI in the previous 12 months. The previous UTI(s) should have resolved prior to a further UTI being diagnosed. Recurrent UTI is one of the most common diagnoses for female pelvic floor dysfunction [3].

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 [4]. Indeed, many patients with recurrent UTIs may have bladder oversensitivity without infection. The prevalence of urinary tract infections (UTIs) and the incidence of urothelial cell carcinoma (UCC) are also higher in patients with ESRD [5]. Among patients with ESRD, the capacity and compliance of the bladder decrease significantly with the duration of dialysis. In one study, abnormal storage function was noted in up to 71% of ESRD patients and bladder outlet obstruction in 51.6%. Vesicoureteral reflux and high postvoid residual (PVR) urine volumes were observed in 110 of 622 (17.5%) and 83 of 62 patients 2 (13.6%), respectively [6]. Although the bladder capacity increased after kidney transplantation and LUTS remained present in only 31 of 622 of patients (4.9%), patients who did not receive kidney transplants still experienced bothersome bladder symptoms [7].

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 [8].

Objectives: The basic aim of the study is to find the Increased chronic urothelial inflammation and its association with urinary tract infection

MATERIAL AND METHODS

This cross sectional study was conducted in Ganga ram hospital, Lahore during June 2020 to December 2020.

Inclusion criteria

1. glomerular filtration rate lower than 30 mL/min
2. Both male and female

Exclusion criteria

- Those who do not want to participate in the study.

Data Collection: The data was collected from 50 patients. Bladder symptoms and lower urinary tract conditions were investigated. All patients were treated actively according to the latest urine culture and followed by antimicrobial prophylaxis for at least 1 month. The bladder biopsies were performed at one to two months after the UTI episode had been completely resolved and urine analysis and urine culture all showed negative. The patients' lower urinary tract symptoms at bladder biopsy were also recorded. All experimental methods were performed in accordance with relevant guidelines and regulations. The urinary bladder specimens were immediately fixed in ice cold 4% formaldehyde phosphate buffered saline (PBS) (pH, 7.4) solution for 1 hour. Next, they were rinsed overnight with ice-cold PBS containing 15% sucrose at 4°C. Then, the specimens were embedded in optimal cutting temperature medium (Miles) and stored at −80°C in liquid nitrogen.

Statistical analysis: The collected data were analyzed using SPSS version 20. The significant value for P <.05 was accepted as statistically significant.

RESULTS

The data was collected from 50 patients. The mean age was 45± 3.56 years for male and 52.3 ± 8.89 years for females. The analysis of data shows the differences in urodynamic variables between the control subjects and the ESRD/CKD patients. Overall, the ESRD/CKD patients had significantly lower FS, US, and CBC than did the controls. Patients with ESRD/CKD with DU had significantly lower FS, CBC in ESRD/DU patients with BO (table 01).

Table 1: Socio demographical variables of patients and control group

Variable	Controls (n = 50)	ESRD/CKD		
		Total	With DU	With BO
Age (yr)	57.9 ± 11.7	59.1 ± 15.0	54.8 ± 11.1	61.0 ± 16.3
FSF (mL)	180.1 ± 65.8	140.2 ± 94.2	63.5 ± 31.8	154.2 ± 95.6
FS (mL)	322.1 ± 81.7	178.3 ± 136.1	66.3 ± 49.6	206.3 ± 137.3*
US (mL)	403.5 ± 104.0	195 ± 133.9	79.3 ± 62.4*	223.9 ± 132.4*
CBC (mL)	404.8 ± 113	204.5 ± 149.1*	79.3 ± 62.4*	235.8 ± 149.2*
Pdet (cm H_2O)	24.4 ± 15.7	26.9 ± 20.0	10.5 ± 9.19	29.7 ± 20.2
Qmax (mL/sec)	18.2 ± 11.6	11.7 ± 11.3	0	13.7 ± 11.1
PVR (mL)	51.8 ± 84.0	104.8 ± 164.5	95 ± 77.8	106.4 ± 177.3
Volume (mL)	363.9 ± 175.1	145.7 ± 130.1*	3.33 ± 5.77*	181.3 ± 120.9*
Pves (cm H_2O)	32.4 ± 17.1	32.8 ± 20.8	28.5 ± 16.3	33.5 ± 22.0

Table 2: Comparison between two groups in structural and functional parameters

Group	Mast cell	TUNEL	α	β
Urothelial inflammation Group	694.88±77.63	0.89±0.13	5.68±1.23	11.25±1.01
Control Group	586.87±62.12	0.96±0.08	4.77±0.62	9.24±1.24
T value	7.818	-3.115	4.712	9.004
P value	0.000	0.002	0.000	0.000

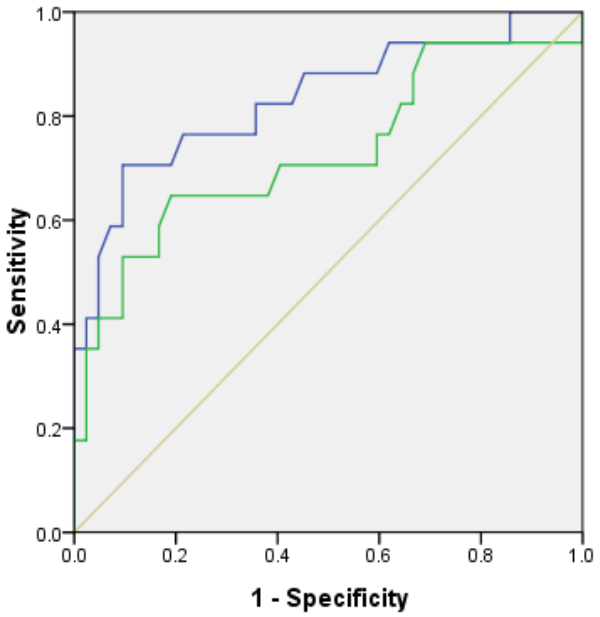

Figure 1: ROC curve of inflammation and UTI in patients

DISCUSSION

In the present study, patients with recurrent UTI had a significantly stronger mast cell expression compared with the normal controls, implied the existence of chronic inflammation in the urothelium. Mast cells, best known for their role in allergic inflammation, are an important source of several inflammatory mediators, including proteases and vasoactive amines such as histamine [9]. Mast cells are considered as crucial effector cells of the immune response implicated in the pathogenesis of IC/BPS.

The bladder urothelium is considered not only to act as a barrier, but also to transmit signals of bladder stretching and noxious stimuli [10]. A previous study showed that the antiproliferative factor presented by the urothelium induced increased membrane permeability in cell cultures; regulated the expression of cytokines, which are linked to enhanced purinergic signaling; and mediated increased bladder sensation [11]. Another study revealed that apoptosis was present in the urothelium of patients with IC and showed that it was possibly regulated by inflammatory pathways. Apoptotic signaling molecules were more common in the bladder tissues of IC patients [12]. The increased apoptosis in the bladder urothelium of IC patients could be due to the upregulation of inflammatory signals. In this study, we observed the same patterns of inflammation, urothelial apoptosis, and barrier deficits in bladder samples from ESRD/CKD patients, suggesting that chronic inflammation might be a fundamental form of pathophysiology in the bladders of these patients [13].

Bladder mast cell activation has been reported as a representative pathological finding in a subset of IC patients. Normal basal cell proliferation could be inhibited by chronic inflammation, which might affect apical urothelial function [14]. In this study, the results of TUNEL staining were correlated with those of tryptase staining, indicating that chronic inflammation of the suburothelium was significantly associated with higher levels of urothelial apoptosis in the bladders of patients with ESRD/CKD [15]. These associations demonstrate that inflammation caused increased apoptosis and affected urothelial sensory function in ESRD/CKD patients [16].

CONCLUSION

It is concluded from our study that increased urothelial inflammation and apoptosis and decreased cell expression were found in patients with ESRD/CKD. Chronic inflammation might reside in the bladder wall after resolution of UTI, which might contribute to urothelial dysfunction and defective barrier function and UTI will be easy to recur in these patients.

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