Abstract #660 Focal or Diffuse Bladder Wall Thickness on Bladder Computed Tomography Indicates More Severe Bladder Wall Inflammation in Patients with Interstitial Cystitis

Tsu-Hsiu Huang, Jia-Fong Jhang, Yuan-Hong Jiang, Wan-Ru Yu, Hann-Chorng Kuo
Department of Urology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, and Tzu Chi University, Hualien, Taiwan

Hypothesis / aims of study

The classification of different phenotypes of interstitial cystitis/ bladder pain syndrome (IC/BPS) provides different pathophysiology and associated treatment strategies. Most clinical studies have focused on bladder symptoms and cystoscopic findings. This study analyzed **bladder wall thickness (BWT)** and compared **bladder conditions**, **urinary biomarkers**, and **histopathology** among patients of IC/BPS with different BWT.

Study design, materials and methods

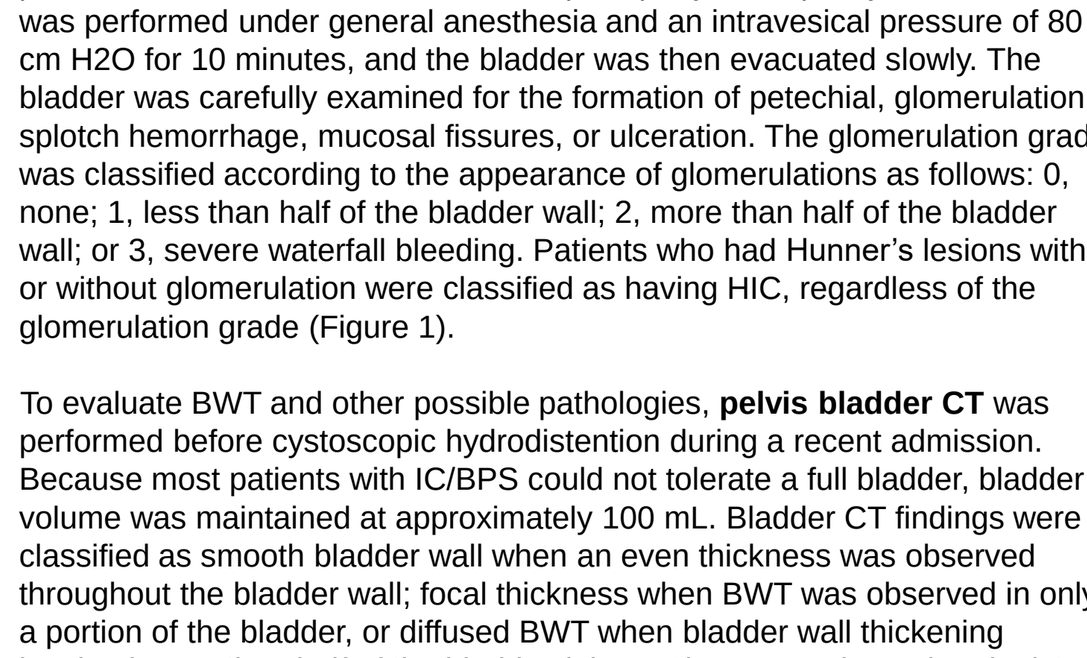
We retrospectively analyzed patients with clinically proven IC/BPS. IC symptom scores, including the IC symptom index, IC problem index, and visual analog scale (VAS) of pain, were recorded at baseline. All patients were thoroughly investigated to confirm the diagnosis of HIC and NHIC based on the presence of Hunner's lesion or glomerulations after cystoscopic hydrodistention without or with anesthesia. Before diagnostic cystoscopy, all patients had also undergone video urodynamic study (VUDS) with a positive KCl test after bladder emptying. The patients also underwent pelvic CT to investigate their lower urinary tract condition and BWT.

To assay urinary inflammatory proteins and oxidative stress biomarkers, urine samples were collected at fullness bladder sensation. In this study, we investigated the following urinary biomarkers: C-X-C motif chemokine ligand 10 (CXCL10); monocyte chemoattractant protein-1 (MCP-1); nerve growth factor (NGF); brain-derived neurotrophic factor (BDNF); exotoxin; interleukin (IL)–2; IL-6; IL-8, macrophage inflammatory protein–1 beta; regulated upon activation, normally T-expressed, and presumably secreted; tumor necrosis factor-alpha (TNF-α); prostaglandin E2; 8-hydroxy-2-deoxyguanosine (8-OHdG); 8-isoprostane; and total antioxidant capacity.

VUDS and cystoscopic hydrodistention were well described in our previous reports. [7,11] The purpose of performing VUDS before cystoscopic hydrodistention was to exclude patients with a normal bladder and the presence of bladder outlet obstruction (BOO). Cystoscopic hydrodistention was performed under general anesthesia and an intravesical pressure of 80 cm H2O for 10 minutes, and the bladder was then evacuated slowly. The bladder was carefully examined for the formation of petechial, glomerulation, splotch hemorrhage, mucosal fissures, or ulceration. The glomerulation grade was classified according to the appearance of glomerulations as follows: 0, none; 1, less than half of the bladder wall; 2, more than half of the bladder wall; or 3, severe waterfall bleeding. Patients who had Hunner's lesions with or without glomerulation were classified as having HIC, regardless of the glomerulation grade (Figure 1).

To evaluate BWT and other possible pathologies, **pelvis bladder CT** was performed before cystoscopic hydrodistention during a recent admission. Because most patients with IC/BPS could not tolerate a full bladder, bladder volume was maintained at approximately 100 mL. Bladder CT findings were classified as smooth bladder wall when an even thickness was observed throughout the bladder wall; focal thickness when BWT was observed in only a portion of the bladder, or diffused BWT when bladder wall thickening involved more than half of the bladder (Figure 1). An experienced urologist (Kuo HC) who was not involved in the final data analysis performed BWT subgrouping in bladder CT.

Figure 1. Characteristic cystoscopic findings and bladder computed tomography in patients with interstitial cystitis. Upper panel: (A) smooth, (B) focal, and (C) diffuse bladder wall thickness. Lower panel: (A) diffuse glomerulations, and (B) (C) presence of Hunner's lesion.



We classified the patients according to different bladder CT subgroups and compared basic demographics, IC symptoms, VUDS findings, and cystoscopic characteristics among patients with smooth, focal, and diffuse BWT. Furthermore, we compared the urinary levels of inflammatory proteins and oxidative stress biomarkers and the histopathological findings from patients with available bladder biopsy and urine specimens among the three BWT subgroups. Thirty women without lower urinary tract dysfunction served as comparative control group and the urine samples were collected for urine biomarkers assay. We evaluated differences in numerical variables using the independent t-test and differences in categorical variables using Pearson's chi-square test and analysis of variance was used to analyze differences among subgroups.

Results and interpretation

Among the studied patients, 85 had smooth, 64 had focal, and 33 had diffuse BWT. The duration of IC history was 9.45 ± 8.56, 9.98 ± 9.98, and 8.03 ± 6.69 years, respectively (p = 0.599). Table 1 shows the clinical demographics, symptoms, and urodynamic parameters of cystoscopic findings in patients with different BWT subgroups. Patients with **diffuse BWT** were significantly **older**, had **smaller MBC** and **cystometric bladder capacity (CBC), higher grade of glomerulation**, and **higher IC symptom scores**. We found HIC in 84.8% of patients with diffuse BWT, 21.9% in patients with focal BWT, and none in patients with smooth BWT. Patients with focal BWT had a higher rate of small MBC than patients with smooth BWT did.

Table 1. Clinical demographics, symptoms, urodynamic findings, and cystoscopic findings in patients with different subgroups of bladder wall thickness.

	Smooth BWT(N=85)	Focal BWT (N=64)	Diffuse BWT(N=33)	P-value and post hoc*
Age (years)	51.8 ± 12.9	57.2 ± 12.0	58.8 ± 14.6	0.007 S v F; S v D
History (years)	9.45 ± 8.56	9.98 ± 9.98	8.03 ± 6.69	0.599
MBC (ml)	836 ± 187	704 ± 187	475 ± 249	0.000 S v F v D
Glomerulation	1.36 ± 0.93	1.62 ± 0.99	2.48 ± 1.09	0.000 S v D; F v D
Hunner's IC	0 (0.0%)	14 (21.9%)	28 (84.8%)	0.000 S v F v D
MBC<760 Gr≧2	20 (23.5%)	15 (23.4%)	3 (9.1%)	0.000
MBC<760 Gr≦1	5 (5.9%)	11 (15.5%)	0 (0.0%)	
MBC≧760 Gr≧2	22 (25.9%)	11 (15.5%)	0 (0.0%)	
MBC≧760 Gr≦1	38 (44.7%)	13 (18.3%)	2 (7.7%)	
FSF (ml)	126 ± 48.5	125±43.2	95.2±55.4	0.000 S v D; F v D
FS (ml)	199 ± 79.5	197 ± 72.5	132 ± 83.8	0.000 S v D; F v D
Compliance	61.1 ± 49.4	69.9 ± 51.3	47.9 ± 64.5	0.162
CBC (ml)	274 ± 112	248 95.5	153 ± 103	0.000 S v D; F v D
Pdet (cmH2O)	19.1 ± 10.0	21.3 ± 14.3	21.6 ± 17.9	0.517
Qmax (ml/s)	11.7 ± 5.85	10.6 ± 5.43	8.50 ± 4.64	0.022 S v D
Volume (ml)	240 ± 112	195 ± 98.1	115 ± 84.7	0.000 S v F v D
PVR (ml)	39.6 ± 79.2	57.9 ± 103	41.8 ± 66.9	0.429
ICSI	12.1 ± 3.99	13.1 ± 4.26	16.1 ± 4.09	0.000 S v D; F v D
ICPI	12.0 ± 3.22	12.0 ± 3.30	14.4 ± 2.65	0.001 S v D; F v D
VAS	5.37 ± 2.58	4.82 ± 3.67	6.59 ± 3.02	0.051

Abbreviations: S: smooth, F: focal, D: diffuse; BWT: bladder wall thickness, MBC: maximal bladder capacity, IC: interstitial cystitis, FSD: first sensation of filling, FS: full sensation, CBC: cystometric bladder capacity, Pdet: detrusor pressure, Gr: grade of glomerulation, Qmax: maximum flow rate, PVR: post-void residual, ICSOI: IC symptom index, ICPI: IC problem index, VAS: visual analog scale of pain

Table 2. Levels of urinary biomarkers in patients with interstitial cystitis and different bladder wall thickness subgroups

	Smooth (N=60)	Focal (N=41)	Diffuse (N=16)	Control (N=30)	P-value	Post hoc*
IL-8	9.56±11.0	11.7±16.8	43.1±58.0	12.5±21.0	0.000	
CXCL-10	4.10±4.28	10.4±13.2	58.8±77.6	13.8±18.4	0.000	S v C
MCP-1	262±239	283±353	289±226	147±110	0.125	
NGF	0.17±0.02	0.17±0.02	0.19±0.06	0.26±0.08	0.000	S v C; F v C; D v C
BDNF	0.55±0.12	0.56±0.12	0.72±0.17	0.55±12	0.000	S v D; F v D; D v C
Exotoxin	8.40±8.57	10.7±10.9	16.5±18.9	4.98±3.70	0.003	F v C
IL-2	0.23±0.06	0.21±0.04	0.21±0.06	0.80±0.19	0.000,	S v C; F v C; F v C
IL-6	1.28±1.58	4.21±6.25	19.7±39.9	1.29±1.35	0.000	
MIP-1β	1.30±1.54	1.68±2.32	5.99±13.3	2.52±1.82	0.006	S v C
RENTES	4.69±5.37	7.74±14.77	9.97±10.3	6.04±5.15	0.264	
TNF-α	1.50±0.37	1.45±0.33	1.95±0.71	0.82±0.33	0.000	S v C; F v C; D v C
PGE2	284±225	267±177	334±380	161±105	0.040	S v C; F v C
8-OHdG	47.4±42.1	34.5±31.5	46.2±43.8	18.0±13.7	0.002	S v C; F v C
8-isoprostane	49.5±33.2	52.6±41.9	42.5±33.1	16.8±11.8	0.000	S v C; F v C; D v C
TAC	1410±1175	1371±1195	1487±1828	1078±925	0.610	

* analysis among smooth, focal, and diffuse BWT; abbreviations: S: smooth; F: focal; D: diffuse BDNF, brain-derived neurotrophic factor; CXCL10, C-X-C motif chemokine ligand 10; 8-OHdG: 8-hydroxy-2-deoxyguanosine; HIC, Hunner's interstitial cystitis; IC/BPS, interstitial cystitis/bladder pain syndrome; IL-, interleukin-; MCP-1, monocyte chemoattractant protein-1; MIP-1β, macrophage inflammatory protein-1 beta; NGF, nerve growth factor; PGE2, prostaglandin E2; RANTES, regulated upon activation, normally T-expressed, and presumably secreted; TAC: Total antioxidant capacity; TNF-α, tumor necrosis factor-alpha

In investigating the **urine biomarker levels** among controls and different IC/BPS patients with different BWT, we found the urinary biomarkers were significantly higher in IC/BPS patients than that of controls in IL-8, CXCL10, exotoxin, IL-6, TNF-α, PGE2, 8-OHdG, and 8-isoprostane. The levels of urinary biomarkers were higher in patients with focal or diffuse BWT than with smooth BWT, in IL-8, CXCL-10, exotoxin, and IL-6. The urinary levels of oxidative stress biomarkers were significantly higher in IC/BPS patients than the controls, but was not significantly different among IC/BPS patients with different BWT (Table 2).

We also investigated the **histopathological findings** of 49 patients of IC/BPS with smooth BWT, 34 with focal BWT, and 26 with diffuse BWT for urothelium denudation, eosinophil and plasma cell infiltration, lamina propria hemorrhage, and granulation and compared these among patients of different BWT subgroups. We found significantly higher rates of mild-to-severe urothelial denudation and presence of plasma cell infiltration in the bladder wall among patients with focal BWT and the highest rates in patients with diffuse BWT as compared with patients with smooth BWT. Patients with diffuse BWT had significantly higher rates of mild-to-severe inflammatory cell infiltration, eosinophil infiltration, nerve bundle hyperplasia, and granulation tissue than those in the smooth and focal BWT subgroups. The other histopathological findings were not different among patients with different BWT subtypes (Table 3).

Table 3. Histopathological findings among patients with interstitial cystitis and different bladder wall thickness subgroups

Histopathology	Severity	Smooth BWT (N=49)	Focal BWT (N=34)	Diffuse BWT (N=26)	P-value
Inflammatory cell infiltration	0, 1 2,3	39 (79.6%) 10 (20.4%)	28 (82.3%) 6 (17.6%)	13 (50%) 13 (50%)	0.039
Urothelial cell denudation	0, 1 2, 3	45 (91.7%) 4 (8.2%)	28 (82.4%) 6 (20%)	11 (44.0%) 15 (56.0%)	0.000
Fibrosis	Present Absent	18 (36.7%) 31 (63.3)	8 (23.5%) 26 (76.5%)	11(42.3%) 15 (57.7%)	0.269
Eosinophil infiltration	Present Absent	7 (14.3%) 42 (85.7%)	5 (14.7%) 29 (85.3%)	11 (42.3%) 15 (57.7%)	0.010
Plasma cell infiltration	Present Absent	8 (16.3%) 41 (83.7%)	7 (20.6%) 27 (79.4%)	13 (50.0%) 13 (50.0%)	0.005
Hemorrhage of lamina propria	Present Absent	3 (6.1%) 46 (93.9%)	2 (5.9%) 32 (94.1%)	4 (16.0%) 21 (84.0%)	0.286
Nerve bundle hyperplasia	Present Absent	1 (2.0%) 48 (98.0%)	0 (0.0%) 34 (100.0%)	5 (19.2%) 21 (80.8%)	0.002
Granulation tissue	Present Absent	5 (10.2%) 44 (89.8%)	3 (8.8%) 31 (91.2%)	15 (60.0%) 10 (40.0%)	0.0001

Conclusions

In patients with IC/BPS, focal and diffuse BWT on bladder CT correlated well with the presence of HIC, small MBC, and high grade glomerulation. The presence of diffuse BWT is associated with increased bladder inflammatory cell infiltration, urothelial cell denudation, eosinophils and plasma cells infiltration, nerve bundle hyperplasia, and granulation tissue in patients with IC/BPS, which might predict the presence of HIC.

References

1. Jhang JF, Hsu YH, Jiang YH, Ho HC, Kuo HC. Clinical Relevance of Bladder Histopathological Findings and Their Impact on Treatment Outcomes among Patients with Interstitial Cystitis/Bladder Pain Syndrome: An Investigation of the European Society for the Study of Interstitial Cystitis Histopathological Classification. J Urol. 2021;205:226-235.
2. Furuta A, Yamamoto T, Suzuki Y, Gotoh M, Egawa S, Yoshimura N. Comparison of inflammatory urine markers in patients with interstitial cystitis and overactive bladder. Int Urogynecol J. 2018 Jul;29(7):961-966.
3. Jiang YH, Jhang JF, Ho HC, Chiou DY, Kuo HC. Urine Oxidative Stress Biomarkers as Novel Biomarkers in Interstitial Cystitis/Bladder Pain Syndrome. Biomedicines. 2022 Jul 14;10(7):1701.
4. Whitmore KE, Fall M, Sengiku A, Tomoe H, Logadottir Y, Kim YH. Hunner lesion versus non-Hunner lesion interstitial cystitis/bladder pain syndrome. Int J Urol. 2019;26 Suppl 1:26-34.