# The X-Y factor: Females and males with urological chronic pelvic pain syndrome present distinct clinical phenotypes

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## Abstract

**Introduction:** Urological chronic pelvic pain syndrome (UCPPS) in females is often attributed to the bladder (interstitial cystitis/bladder pain syndrome), while UCPPS in males is often attributed to the prostate (chronic prostatitis/chronic pelvic pain syndrome). However, there is increasing awareness that bladder pain plays a role in both males and females and the degree of overlap of clinical characteristics in males and females with UCPPS is not well known. Our objective was to compare clinical phenotypes of females and males with UCPPS.

**Methods:** We conducted a retrospective analysis of prospectively collected data from a single-centre patient population presenting between 1998 and 2016 to our UCPPS clinic. Demographics, symptom scores, pain scales, retrospectively described clinical UPOINT (urinary, psychosocial, organ-specific, infection, neurogenic, and tenderness) scoring, and presence of comorbid medical conditions were compared between females and males using comparative analyses.

**Results:** We identified 2007 subjects (1523 males, 484 females) with UCPPS. Females had increased prevalence of irritable bowel syndrome (25% vs. 11.2%), chronic fatigue syndrome (13.6% vs. 1.6%), fibromyalgia (16.9% vs. 1.6%), drug allergies (56.6% vs. 13.5%), diabetes (20.2% vs. 3.9%), depression (31% vs. 18.4%), and alcohol use (44.2% vs. 10.8%) compared to males with UCPPS (all $p<0.001$). In respect to UPOINT domains, females had a higher "total" (3.2 vs. 2.4), "urinary" (92.8% vs. 67.6%), "organ-specific" (90.1% vs. 51.4%), and "neurogenic" (44.7% vs. 30%) prevalence compared to males (all $p<0.001$).

**Conclusions:** Females with UCPPS have greater prevalence of systemic disorders/symptoms and worse urinary symptoms than males with UCPPS. These findings demonstrate that females and males with UCPPS have distinct and different clinical phenotypes.

## Introduction

Urological chronic pelvic pain syndrome (UCPPS) refers to chronic and often debilitating pain in the pelvis, prostate, bladder, and/or genitalia.[1] UCPPS encompasses interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).[1] IC/BPS is defined as persistent or recurrent chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as urgency or frequency.[2] CP/CPPS is defined as chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland.[3] Although UCPPS in males is often attributed to the prostate (CP/CPPS) and UCPPS in females is often attributed to the bladder (IC/BPS), there is increasing awareness that males may also have bladder involvement.[4,5] In a population screening study, 48% of males screened positive for IC/BPS using a high-specificity definition of IC/BPS, and a further 18% screened positive for both CP/CPPS and IC/BPS.[4] This has led some to propose that IC/BPS and CP/CPPS may represent analogous conditions in females and males, respectively.[6-8]

To date, there have been limited studies comparing clinical characteristics of UCPPS in males and females. Using the MAPP database, Clemens et al found variation in rates and severity of bladder symptoms among females and males with UCPPS.[9] Also using the MAPP database, Lai and colleagues found that those who had a subtype of UCPPS with pain outside of the pelvis had higher rates of fibromyalgia (FM), chronic fatigue syndrome (CFS), and irritable bowel syndrome (IBS) compared to those with pain limited to the pelvis.[10] However, they did not compare rates of FM, CFS, and IBS among females and males. UPOINT (urinary, psychosocial, organ-specific, infection, neurogenic, and tenderness) scoring has been shown to be a useful clinical tool for phenotyping males with CP/CPPS[11] and females with IC/BPS,[12] as well as for guiding treatment decisions. Our objective was to compare the entire clinical phenotypes of males and females presenting with UCPPS to a single tertiary

referral centre by examining urinary and pain symptoms, UPOINT scores, and associated medical conditions. To further characterize sex-based phenotypic differences among patients with UCPPS, we compared a subgroup of males with IC/BPS to females with IC/BPS.

## Methods

### Participants and study design

This is a retrospective evaluation of a large, prospective, clinical quality assurance database of patients with IC/BPS and CP/CPPS treated at our outpatient clinic by a single urologist (JCN) between 1998 and 2016. Our IC/BPS patient sample has been described in previous publications.[13] Briefly, patients were diagnosed with IC/BPS on the basis of chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as urgency or frequency. Exclusion criteria included positive urine culture or cytology. All other diseases that could cause pelvic symptoms were excluded with our standardized history and physical examination, which included a pelvic examination. Our male CP/CPPS patient sample has also been described in previous publications.[14,15] These included male patients referred by both primary care physicians or urologists to the Queen's University Prostatitis Research Centre who have fulfilled the National Institutes of Health/National Institute for Diabetes and Digestive and Kidney Diseases criteria for a diagnosis of CP/CPPS.[16] Briefly, these would include men with pelvic pain for three of the previous six months, with or without voiding symptoms, and with no evidence of uropathogenic bacterial infection.

This retrospective study was done under ongoing institutional review board approval for continued quality assurance, with all patient data de-identified before analysis.

### Measures

Data on patient demographics, symptom duration, urinary frequency scores (0–5), pain frequency scores (0–5), pain severity (0–10), clinical UPOINT scoring (retrospectively determined on patients assessed prior to 2009), and the presence or absence of comorbid medical conditions (FM, IBS, CFS, diabetes, depression, alcohol use, food/drug allergies, and hypertension) were collected through initial evaluations at the IC/BPS and CP/CPPS outpatient clinics. IBS diagnosis was made based on the Rome III criteria. Patient self-report questionnaires assessed presence of the remaining conditions. UPOINT descriptions have been previously published.[11,12]

### Data analysis

Statistical analysis was completed using the Microsoft Excel 2010 Data Analysis package and the Social Science Statistics (*http://www.socscistatistics.com/*). In all cases, statistical analysis was done between male and female cohorts. Categorical data, including UPOINT domains and the presence or absence of comorbid medical conditions, were analyzed using the two-tailed z-test for population proportions. Other quantitative data, age, symptom duration, and all questionnaire scores were analyzed using the two-tailed t-test and assuming unequal variances. All results considered statistically significant at $p<0.05$.

## Results

We identified 2007 subjects (1523 males, 484 females) with UCPPS. Of the 1523 male patients, 26 had IC/BPS and seven had Hunner lesions identified on cystoscopy. Of the 484 female patients with IC/BPS, 41 had Hunner lesions identified on cystoscopy. Table 1 shows a comparison of demographics, symptom scores, UPOINT scores, and medical comorbidities. Females had statistically significantly longer symptom duration (at time of referral to the tertiary urology pain clinic) compared to males (10.7 vs. 6.75 years; $p<0.001$). While females reported significantly higher scores for urinary frequency (4.0±1.3 vs. 2.7±1.7; $p<0.001$) and pain frequency (3.2±1.5 vs. 3.0±1.5; $p<0.001$), males reported higher pain intensity scores (4.6±2.7 vs. 4.1±3.6; $p=0.006$).

When comparing prevalence of UPOINT domains, females had a higher total prevalence compared to males (3.2 vs. 2.4; $p<0.001$). Specific UPOINT domains that were more prevalent in females were "urinary" (92.8% vs. 67.6%; $p<0.001$), "organ-specific" (90.1% vs. 51.4%; $p<0.001$), and "neurogenic" (44.7% vs. 30%; $p<0.001$). Females had a lower prevalence of UPOINT "tenderness" (42.7% vs. 48.6%; $p=0.02$) and "infection" (21.1% vs. 32.8%; $p<0.001$) domains compared to males.

There were notable differences in the presence of comorbid medical conditions as well. Females were found to have a higher prevalence of FM (16.9% vs. 1.5%; $p<0.001$), CFS (13.6% vs. 1.6%; $p<0.001$), IBS (25% vs. 11.2%; $p<0.001$), drug allergies (56.6% vs. 13.5%; $p<0.001$), diabetes (20.2% vs. 3.9%; $p<0.001$), depression (31% vs. 18.4%; $p<0.001$), and alcohol use (44.2% vs. 10.8%; $p<0.001$) compared to the male cohort.

A subgroup analysis of males diagnosed with IC/BPS compared to females with IC/BPS was performed (Table 2). Females with IC/BPS were younger than males with IC/BPS at time of presentation (45.7 vs. 58.5 years; $p<0.001$). In respect to UPOINT domain prevalence, the female IC/BPS patients had higher "infection" (21.1% vs. 0%; $p=0.009$) and "neurogenic" (44.7% vs. 23.1%; $p=0.03$) domain prevalence

**Table 1. Comparison of males and females presenting with urological chronic pelvic pain syndrome**

| | n | Female | n | Male | p |
|---|---|---|---|---|---|
| Age and symptoms, mean ± SD | | | | | |
| Age at presentation (years) | 484 | 45.7±17.4 | 1523 | 45.1±13.5 | 0.47 |
| Symptom duration (years) | 367 | 10.7±11.7 | 1238 | 6.75± 8.6 | <0.001 |
| Urinary frequency (0–5) | 466 | 4.0±1.3 | 1431 | 2.7±1.7 | <0.001 |
| Pain frequency (0–5) | 466 | 3.2±1.5 | 1431 | 3.0±1.5 | <0.001 |
| Pain intensity (0–10) | 464 | 4.1±3.6 | 1431 | 4.6±2.7 | 0.006 |
| UPOINT | | | | | |
| Total (0–6), mean ± SD | 483 | 3.2±1.4 | 1516 | 2.4±1.2 | <0.001 |
| Urinary, n (%) | 483 | 448 (92.8) | 1523 | 1029 (67.6) | <0.001 |
| Psychosocial, n (%) | 483 | 153 (31.7) | 1523 | 427 (28.0) | 0.12 |
| Organ-specific, n (%) | 483 | 435 (90.1) | 1523 | 783 (51.4) | <0.001 |
| Infection, n (%) | 483 | 102 (21.1) | 1523 | 499 (32.8) | <0.001 |
| Neurogenic, n (%) | 483 | 216 (44.7) | 1523 | 457 (30.0) | <0.001 |
| Tenderness, n (%) | 483 | 206 (42.7) | 1523 | 740 (48.6) | 0.02 |
| Medical history, n (%) | | | | | |
| Fibromyalgia | 484 | 82 (16.9) | 1523 | 23 (1.5) | <0.001 |
| Chronic fatigue syndrome | 484 | 66 (13.6) | 1523 | 25 (1.6) | <0.001 |
| Irritable bowel syndrome | 484 | 121 (25) | 1523 | 170 (11.2) | <0.001 |
| Drug allergies | 484 | 274 (56.6) | 1523 | 205 (13.5) | <0.001 |
| Food allergies | 484 | 67 (13.8) | 1523 | 174 (11.4) | 0.15 |
| Diabetes | 484 | 98 (20.2) | 1523 | 59 (3.9) | <0.001 |
| Depression | 484 | 150 (31) | 1523 | 280 (18.4) | <0.001 |
| Hypertension | 484 | 85 (17.6) | 1523 | 844 (55.4) | <0.001 |
| Alcohol use | 484 | 214 (44.2) | 1523 | 165 (10.8) | <0.001 |

SD: standard deviation.

compared to males with IC/BPS. Furthermore, the females had a higher prevalence of IBS (25% vs. 3.8%; p=0.01) and drug allergies (56.6% vs. 30.8%; p=0.01) compared to males with IC/BPS. Due to the low number of males with IC Hunner lesions (n=7), we did not compare males and females with IC Hunner lesion phenotype.

## Discussion

As there is increasing awareness that UCPPS in males may relate not only to the prostate, more have argued that IC/BPS and CP/CPPS may represent different manifestations of the same disease process.[6-8] However, data comparing clinical characteristics of UCPPS in males and females has been lacking. In this retrospective analysis of prospectively collected data on a large, single-centre patient population, we show several important differences, including a much higher prevalence of comorbid medical conditions, greater prevalence of UPOINT domains, and worse urological symptoms in females compared to males with UCPPS.

Although it is well-established that males and females with UCPPS have increased prevalence of comorbid functional/systemic symptoms compared to healthy controls,[17-19] there have been no studies to date directly comparing the presence of comorbid functional/systemic conditions among males and females with UCPPS. We found that females had increased prevalence of IBS (25% vs. 11.2%), CFS (13.6% vs. 1.6%), and FM (16.9 vs. 1.6%) compared to males with UCPPS. Females also had increased prevalence of drug allergies (56.6% vs. 13.5%), diabetes (20.2% vs. 3.9%), depression (31% vs. 18.4%), and alcohol use (44.2% vs. 10.8%) compared to males with UCPPS. Females in the general population are known to have increased prevalence of FM, CFS, and IBS compared to males, with female to male ratios of approximately 6:1,[20] 2:1,[21] and 3:1,[22] respectively. We found that females in our study with UCPPS had increased prevalence of FM, CFS, and IBS beyond that expected in non-UCPP populations, with female to male ratios of 11:1, 9:1, and 15:1, respectively. There is increasing awareness that patients with pain symptoms outside of the pelvis may represent a different clinical phenotype than those with pain limited to the pelvis.[10,19,23] Patients with pain outside of the pelvis are hypothesized to have increased sensitization of central pain processing pathways leading to higher co-occurrence of other systemic pain conditions, such as IBS, CFS, and FM, while, in patients with pain limited to the bladder, pain has been hypothesized to occur through visceral nerve abnormalities involving only the bladder.[23] Lai and colleagues found that those with pelvic pain and beyond phenotype had higher rates of FM, CFS, and IBS compared

**Table 2. Comparison of females with IC/BPS to a subset of males with IC/BPS**

| | n | Female | n | Male | p |
|---|---|---|---|---|---|
| Age and symptoms, mean ± SD | | | | | |
| Age at presentation (years) | 484 | 45.7±17.4 | 26 | 58.5±13.0 | <0.001 |
| Symptom duration (years) | 367 | 10.7±11.7 | 22 | 7.6±6.8 | 0.55 |
| Urinary frequency (0–5) | 466 | 4.0±1.3 | 23 | 4.1±1.5 | 0.66 |
| Pain frequency (0–5) | 466 | 3.2±1.5 | 23 | 2.8±1.7 | 0.21 |
| Pain intensity (0–10) | 464 | 4.1±3.6 | 26 | 4.2±3.9 | 0.94 |
| UPOINT | | | | | |
| Total (0-6), mean ± SD | 483 | 3.2±1.4 | 26 | 2.5±0.9 | <0.001 |
| Urinary, n (%) | 483 | 448 (92.8) | 26 | 25 (96.2) | 0.51 |
| Psychosocial, n (%) | 483 | 153 (31.7) | 26 | 6 (23.1) | 0.12 |
| Organ-specific, n (%) | 483 | 435 (90.1) | 26 | 24 (92.3) | 0.71 |
| Infection, n (%) | 483 | 102 (21.1) | 26 | 0 (0) | 0.008 |
| Neurogenic, n (%) | 483 | 216 (44.7) | 26 | 6 (23.1) | 0.03 |
| Tenderness, n (%) | 483 | 206 (42.7) | 26 | 4 (15.4) | 0.06 |
| Medical history, n (%) | | | | | |
| Fibromyalgia | 484 | 82 (16.9) | 26 | 1 (3.8) | 0.078 |
| Chronic fatigue syndrome | 484 | 66 (13.6) | 26 | 1 (3.8) | 0.14 |
| Irritable bowel syndrome | 484 | 121 (25) | 26 | 1 (3.8) | 0.014 |
| Drug allergies | 484 | 274 (56.6) | 26 | 8 (30.8) | 0.01 |
| Food allergies | 484 | 67 (13.8) | 26 | 2 (7.7) | 0.37 |
| Diabetes | 484 | 98 (20.2) | 26 | 4 (15.4) | 0.55 |
| Depression | 484 | 150 (31) | 26 | 4 (15.4) | 0.09 |
| Hypertension | 484 | 85 (17.6) | 26 | 7 (26.9) | 0.23 |
| Alcohol use | 484 | 214 (44.2) | 26 | 11(42.3) | 0.85 |

IC/BPS: interstitial cystitis/bladder pain syndrome; SD: standard deviation.

to those with pain limited to the pelvis.[10] However, they did not compare rates of FM, CFS, and IBS between females and males. Our results indicate that gender itself may represent a distinct clinical phenotype in which females have greater prevalence of systemic pain/neural conditions. Hypersensitivity of peripheral and central pain processing pathways has been hypothesized to be a sex-biased consequence of chronic stress in females.[24] This may underlie our findings of higher prevalence of somatic symptoms in females with UCPPS compared to males.

Interestingly, we found that females with UCPPS had higher rates of alcohol use compared to males with UCPPS, whereas the opposite is true in the general population.[25] This may be related to higher rates of depression and psychological stress in females compared to males with UCPPS, which have been associated with alcohol use.[26] Prior studies have reported decreased rates of diabetes in patients with IC/BPS, however, in our study there was a significantly higher rate of diabetes in our female UCPPS population compared to rates reported in the general population (20% vs. 6%).[27] The reason for this discrepancy is unclear.

UPOINT has been shown to be a useful clinical tool for phenotyping males with CP/CPPS[11] and females with IC/BPS,[12] as well as for guiding treatment decisions; however, no study to date has directly compared prevalence of UPOINT domains among males and females with UCPPS. Using UPOINT, we found an increased prevalence of "urinary," "organ-specific," and "neurogenic" domains in females compared to males with UCPP, and increased "infection" and "tenderness" domains in males compared to females. The prevalence of UPOINT domains for males and females in the current study were similar to previous studies.[11,12] As the criteria for diagnosis of IC/BPS in the current study included perceived bladder pain and the presence of at least one urinary symptom, the "urinary" and "organ-specific" domains would be expected to be more prevalent based on diagnostic criteria alone.

While UPOINT domain prevalence between females with IC/BPS and the subgroup of males with IC/BPS were more similar, females with IC/BPS still had increased prevalence of "neurogenic" domains compared to males with IC/BPS. As far as we know, we are the first group to compare clinical phenotypes of females with IC/BPS and males specifically with IC/BPS. This is an important finding that indicates that sex-based phenotypic differences reported here and elsewhere cannot only be attributed to involvement of the prostate in males.

Similar to our findings of increased urinary and pain frequency among females compared to males with UCPPS, Clemens et al found that females with IC/BPS had significantly worse urgency, frequency, and nocturia.[9] In their pro-

spective study comparing 233 females to 191 males, females reported higher scores on Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), and American Urological Association Symptom Index (AUASI), compared to males with CP/CPPS.[9] In a large, prospective survey study of 981 females and 1768 males, Marszalek et al also found that women had a greater prevalence of storage urinary symptoms as measured on the Chronic Prostatitis Symptom index (CPSI) and International Prostate Symptom Score (IPSS), compared to males.[28]

The findings of the current study have implications for our understanding and management of UCPPS in males and females. Different symptom patterns and clinical phenotypes suggest different etiologies and pathogenic pathways between the sexes. There is evidence that therapy directed at clinical UPOINT phenotypes leads to increased treatment success for IC/BPS[13] and CP/CPPS.[11] It is likely that therapies directed at "urinary" (antimuscarinics, pyridium, bladder retraining), "organ-specific" (pyridium, intravesical glycosaminoglycans, dimethyl sulfoxide, lidocaine, pentosan polysulfate sodium, quercetin) and "neurogenic" (amitriptyline, gabapentinoids, system-specific therapies, specialist referral for systemic disorders) domains may be more effective overall in the female UCPPS population compared to males. In contrast, therapies directed at the "infection" (antimicrobials) and "tenderness" (pelvic floor physiotherapy, muscle relaxants, trigger point injections) domains may be more effective in the male UCPPS population compared to females. That being said, an individualized treatment approach should be taken based on each patient's unique clinical phenotype.

Limitations of the current study include the retrospective analysis (although data was collected prospectively). Patient self-report was used for all conditions other than IBS, allowing for the possibility that prevalence would differ using specific diagnostic criteria. Additionally, this was a single-centre study, which could limit external validity. Strengths of our study include the large study population, prospective data collection, and our use of Rome III diagnostic criteria for IBS.

## Conclusion

Females with UCPPS have worse urinary symptoms and greater prevalence of systemic disorders/symptoms, including IBS, CFS, and FM, as well as increased prevalence of the UPOINT "urinary," "organ-specific," and "neurogenic" domains compared to males with UCPP. Males exhibited increased prevalence of the "infection" and "tenderness" domains. These findings demonstrate distinct male and female phenotypes in patients with UCPPS.

**Competing interests:** Dr. Nickel has been a consultant for Astellas, Auxillium, Eli Lilly, Farr Labs, Ferring, GSK, Pfizer, Redleaf Pharma, Taris Biomedical, Tribute, and Trillium Therapeutics; a lecturer for Astellas and Eli Lilly; and has participated in clinical trials supported by Eli Lilly, GSK, J&J, Pfizer, and Taris Biomedical. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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