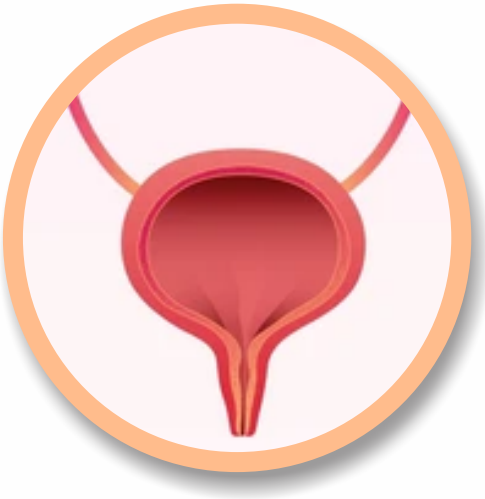
GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

Volume 4 Issue 10 November 2022

GIBS News Letter



URINARY BIOMARKERS IN IC/BPS

Interstitial cystitis/ Bladder pain syndrome (IC/BPS) is a chronic condition characterised by pain (suprapubic or pelvic) and discomfort related to bladder filling. The symptoms of IC/BPS patientsoften coexist with insomnia, depression, anxiety and sexual dysfunction, thereforeresulting in impaired quality of life and withdrawal from social activities. Notwithstanding the advancement in our understanding of the disease, the exact pathophysiology of this entity is still elusive. Thinking compassionately for the patients who suffer from this illness, I think they are hit by a double whammy: the pain and suffering because of the disease itself and the pain and anxiety caused by the lengthy diagnostic procedures which presently is aimed to rule out other confusable diseases. The entire experience can be overwhelming and devastating for any patient. Hence the search for a simple and reliable diagnostic marker for IC/BPS is an ongoing quest. Today we may be far from attaining one but our quest must go on. Urinary biomarkers are one such diagnostic tools which are garnering a lot of interest from the researchers these days. They are like a ray of hope which presently may seem a distant dream but the days may not be far when they become the mainstream diagnostic tests. With this hope and an eye towards the future let us now understand what are the various urinary biomarkers which may be useful in IC/BPS.

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Biomarker is short for biological marker, and is used as an indication that a biological process in the body has happened or is ongoing. The use of urinary biomarkers to diagnose disease has been a long-standing practice. Ancient clinicians detected glucose in the urine by tasting it or observing whether it attracted ants. The presence of albumin in the urine has been measured as an indicator of renal disease for centuries and in early times could be detected via the so-called "foam test" to determine whether albumin was present in the urine in large amounts. We have come a long way since those times. The basic premise for the development of research on urine for diagnosis of various bladder conditions is that the urine remains in contact with the bladder mucosa and would thereby carry some biomarkers which would point towards a diagnosis. And moreover, urine is a sample which can easily be collected without any needle prick and hence allows for easy multiple sampling. It has also been seen that urine as a sample has greater stability over serum or blood. These characteristics make urine a promising sample for these kinds of futuristic researches. For IC/BPS, urinary biomarkers are being developed to facilitate its diagnosis (including the differentiation between Hunner Lesion type of IC/BPS (HIC) and non Hunner lesion type (NHIC)) and objective follow-up.

Proteomic biomarkers: Proteomic profiling of the urine revealed several cytokines and chemokines which were associated with IC/BPS and could possibly serve as useful tools to assess treatment outcomes. Proper function of the urothelium requires normal epithelial integrity, which relieson intercellular adhesion molecules and a layer of molecular components on theapical surface of the urothelium, which is composed of GAG. Abnormal expressionsof urothelial-associated proteins, including zonula occludens type 1 (ZO-1), E-cadherin,uroplakin, chondroitin sulfate, and receptors/ion channels have been noted in IC/BPSbladders on bladder biopsy specimens. Uroplakins (UPK) are a family of integralmembrane proteins of bladder urothelium. Overexpression of uroplakin III has also beenshown in bladder of NHIC/BPS. In an animal model of experimental autoimmunecystitis, injection of UPK3A has been shown to induce T-cell attack on the bladder epithelium,resulting in chronic suprapubic hypersensitivity and other symptoms that mimichuman IC/PBS disease. These abnormal alterations may help disrupt urethral barrierand sensory functions, leading to increased afferent nerve activity and manifesting bladdersymptoms such as hypersensitivity, pain, or urgency. Increased levels of UPK3A has been found in urine samples and being investigated as a potential biomarker for IC/BPS.

Erickson et al.1 and Sakthivel et al.2 found that several proinflammatorymediators, such as interleukin-6 (IL-6) and CXC chemokines, were increased in both urinaryand serum samples of IC/BPS patients.

Magalhaes et al3had published an excellent review on the subject in 2019 and had described these biomarkers. The urinary biomarkers discussedin the study included macrophage inhibitory factor (MIF), nerve growth factor (NGF), methylhistamine, histamine, IL-6, antiproliferative factor (APF), epithelial growth factor (EGF), heparin-binding (HB)- EGF and glycoprotein G5P1. Urinary MIF was studied by Vera et al.4and they verified that urinary MIF was significantly higher in IC/BPS patients with Hunner lesion compared with patients without Hunner lesions and with controls. Patients with lower urinary tract diseases, including stones, tumors,acute bacterial infection, IC/BPS and bladder outlet obstruction,have been found to have increased NGF levels in the urine, serum, and/or bladder tissue. In thebladder, NGF is expressed in the urothelium, smooth muscle, afferent nerves, and ganglia. NGF acts as a chemical mediator in C-fibre afferents that may regulate urinarybladder function. Current findings suggested that the urinary NGF level can bemonitored as a biomarker for IC/PBS severity and for treatment response. In a transgenicmouse model, NGF overexpression in the bladder led to neuronal hypersensitivity andchanged in urinary bladder function. In samples of patients with IC/BPS, increasedlevels of NGF have been noted in the urine and bladder tissue. TheNGF level of serum and urinary in IC/BPS patients was elevated, while the level was alsonot related to the severity of IC/BPS. The urinary NGF level has been shown to beclosely related to the visual analogue scale (VAS) score for inflammatory pain and treatmentoutcome for IC/BPS. Clinical and experimental data in IC/BPS have indicated correlationbetween increased levels of NGF in the bladder tissue and urine and painful inflammatory conditions. These findings suggested that NGF is associated with bladder function, andelevated urinary NGF levels reflect that chronic inflammation occurs in the urinary bladderof IC/BPS patients. NGF might be developed as an indicator for treatment, in order to be asensitive molecular diagnostic tool for IC/BPS5.

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Also, assessing both urine and bladder biopsy samples, Corcoran et al.6determined the profile of 23 chemokines in 10 patients with BPS and 10 asymptomatic controls. In urine, univariate analysis showed no significant differences in any of the proteins assessed, but multivariate analysis revealed that

VCAM-1 and ICAM-1 were responsible for the discrimination of urine of IC/BPS patients from that of controls.Lamale et al.7 investigated urinary histamine, IL-6, and methylhistamine in IC/BPS patients and controls. They found that urinary concentrations of histamine and IL-6 were increased in IC/BPS patients. However, methylhistamine levels had no significant differences between IC/BPS patients and controls. Further logistic regression analysis demonstrated that the best predictor for IC/BPS was a combined model with IL-6 and methylhistamine. According to this model, BPS diagnosis could be established in the following scenarios: lL-6 levels above 2.28 pg/mL regardless of methyl-histamine levels; methylhistamine concentration above 288 pg/mL regardless of IL-6 levels; or IL-6 below 2.28 pg/mL, but methylhistamine levels equal to or higher than 126.56 pg/mL multiplied by the difference between 2.28 and IL-6 levels. This model showed 70% sensitivity, 72.4% specificity, 77.8% positive predictive value, and 63.6% negative predictive value.

Both OAB and IC/BPS might share acommon pathway, for example, mast cell infiltration was found in both diseases. However,abnormal urothelial barrier function only occurred in IC/BPS patients, but not in those withOAB. Urine CXCL-10 is elevated in patients with IC/BPS, but not in OAB patients8. The upregulated levels of serum TNF- α, IL-1, 6, and 8, and urine CXCL-10 level in IC/BPSpatients might help provide as an appropriate diagnostic tool. The increased expression ofproinflammatory cytokines and chemokine levels in the serum of IC/BPS patients indicatedthat not only the activation of mast cell, but also inflammatory mediators might play keyroles in the pathogenesis of IC/BPS. Serum CRP is elevated in patients with LUTSand IC/BPS. The CRP levels ofserum and urine might serve as a biomarker of local bladder inflammation to distinguishpatients with IC/BPS.

Keay et al.9 found that APF was increased in IC/BPS patients compared to controls, but HB-EGF concentrations were decreased in IC/BPS patients. APF glycoprotein is secreted by bladder urothelial cells from IC/BPS patients and slows down the growth of urothelial cells. APF may mediate the pathological changes observed in IC/BPS, including inhibition of cell growth, increased barrier permeability and reduced proteins expression (e.g., cadherins), while promoting the formation of intercellular complexes. Increased susceptibility to urothelial damage may bedue to altered factors that regulate the development of structural elements. Therefore, the seproteases have been proposed as potential biomarkers or to provide assessment of disease progression but have not been validated in lower urinary tract disorders. An increased APF and lower expression of IL-8 have been found in IC/BPS bladders, which may contributeto IC/BPS pathophysiology. Furuta et al10 suggested that increased levels of VEGF in urine may signal increased angiogenesis in the bladder which in turn is suggestive of VEGF induced

bladder fibrosis, and reduced bladder capacity after chronic inflammation. This VEGF is also being explored as a potential biomarker for the prognosis and as a marker for assessing treatment outcomes.

ATP is released from urothelium in response to bladder stretch and could act onurothelial purinergic receptors. Patients with IC/BPS have increased afferent nerve densityand ATP release, which might affect the symptoms of pain, urgency and frequency. Studies also suggest that ATP release may influence function of myofibroblasts and afferent nerveendings [158]. In patients with IC/BPS, urinary ATP levels were significantly higher than control [159]. Blocking ATP release improved the symptoms of pain, urgency, and frequency for IC/BPS patients. Similar to the data in human IC/BPS, a significant increasein stretch-evoked ATP release in IC/BPS feline model [160] and in CYP-induced rats caused chronic bladder inflammation [161].

Not all biomarkers are increased in patients with IC/BPS. The pathophysiology of IC/BPS urothelium is involved in an aberrant synthesis of bacterial defence molecules such as GP51 and Byrne et al.11 demonstrated that the level of urinary glycoproteinGP51 secreted from urothelial cells was reduced in IC/BPS patients.

Lee and co-workers12 investigated ß-defensin 2, which is an antimicrobial peptide normally expressed in the bladder upon inflammation and persistently expressed

in IC/BPS. In their study, the authors compared the urine BD-2 levels in three female groups, normal controls, non-Hunner-type IC (NHIC) and Hunner-type IC (HIC). They found significant higher BD-2 levels in the HIC group than in the control or NHIC. Those expression levels correlated with higher mast cell counts in HIC. These finding further support our understanding of HIC as a chronic inflammation condition, possibly altering the bladder microbiota.

Metabolomic Biomarkers: At present, urinary metabolomic biomarker studies are primarily conducted either by Nuclear magnetic resonance (NMR) spectroscopy or liquid chromatography mass spectrometry (LQ-MS)-based identification. Using liquid chromatography-MS in urine samples of 40 women with BPS and 40 controls, principal component analysis by Parker et al.13 demonstrated there to be two distinctmetabolomic profiles in women with BPS.The

first(G1) had a profile similar to controls, which was distinct fromthe metabolomic profile of the second (G2). To determineexactly which metabolites and classes of metabolites coulddistinguish patients in subgroup G2 from the others, the authors used graphic representations and found six metabolitesmost closely associated with IC/BPS. One of them was a molecule highly abundant in G2 samples, found at a chromatographic peak of 369 m/z, which corresponded to Etio-S.Analysis of variance comparing Etio-S levels in the twoBPS subgroups and controls showed that the correlation reported was statistically significant; and a validation study determined that elevated Etio-S is a good predictor of IC/BPS, with91.2% sensibility, 87.4% specificity, and 0.92 AUC. In thelongitudinal analysis of women in this cohort, differences inEtio-S persisted, showing that these changes are long-lasting.

DNA methylation biomarkers for IC: In their research Magalhaes et al. foundthat DNA methylation in urine samples was associated withIC/BPS. Bradley et al14 determined DNA methylationprofiles in IC/BPS and controls. They found thatthere was no genome-scale significantly different methylationin CpG sites. Among the methylated CpG sites, the mostprominent enrichment pathway was the mitogen-activatedprotein kinase (MAPK) pathway. This pathway had 86% ofsites with hypomethylation in IC/BPS patients compared tothe controls.There is evidence that DNA methylation biomarkersare more sensitive than cytology although there were biomarkerstested on cohorts that varied between studies. A highly selectiv panel of methylation biomarkers may increase the sensitivity and specificity of urine analysis in the clinical studies15.

Clinical observations imply that IC/BPS develops over a long time and that thesymptoms in early stages are mostly misdiagnosed as related urinary tract diseases. Biomarkers able to discriminate between confusable diseases and IC/BPS at early stages would be of great value for early onsetof specific treatment. Despite our steadily increasing knowledge on the molecular and cellular mechanisms involved in the pathophysiology of IC/BPS, we are still far from understanding this disease. The great spectrum of IC/BPS biomarkers currently under evaluation raises hope that we can develop panels of biomarkers for early detection, stratification, and treatment assessment in future.

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