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REVIEW ARTICLE

Biomarkers in the diagnosis and symptom assessment of patients with bladder pain syndrome: a systematic review

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Abstract

Introduction and hypothesis Bladder pain syndrome (BPS) is a disease of unknown etiology defined as an unpleasant sensation related to the bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of any identifiable causes. Despite its impact on quality of life (QoL) and socioeconomic burden, there are no objective methods for the diagnosis or assessment of therapeutic response. We systematically reviewed biomarkers associated with BPS to update the current knowledge on this issue.

Methods A systematic review of the Cochrane Library, Embase, PubMed/MEDLINE, LILACS, SCOPUS, and ClinicalTrials.gov databases was conducted following the PRISMA statement. Original articles investigating biomarkers for the diagnosis or symptom assessment of patients with BPS were assessed; no language restrictions were applied. Animal or post-mortem studies were excluded.

Results Of the 478 records retrieved, 11 articles were included. MIF, NGF, Etio-S, APF, and a combined methylhistamine/Il-6 model were increased in BPS urine samples versus controls. Also increased were glyceraldehyde in stool, in addition to the expression of some genes (ARID1A, ARF, CHAT, eNOS, GLI-1, iNOS, MCP-1, NGF, WNT-8A, WNT-10A), nerve density, IL-16, VCAM-1, and ICAM-1 in bladder tissue specimens. In contrast, some fecal bacteria, expression of other genes (CHT, HB-EGF, OCT-1, SMRT-1, WNT11) in the bladder urothelium, and urinary DNA methylation in CpG-sites, MCP-3, G5P1, and HB-EGF were decreased in BPS. As none of the biomarkers was studied more than once, a Forest plot could not be constructed. Only 4 articles reported the relation of biomarkers to symptom scores.

Conclusions Potential biomarkers for BPS in urine, stool, and bladder biopsy specimens are described. Further research is needed before their use in clinical practice.

Keywords Interstitial cystitis · Diagnosis · Signs and symptoms

Introduction

Bladder pain syndrome (BPS) is defined as an unpleasant sensation (pain, pressure or discomfort), related to the bladder, in the presence of lower urinary tract symptoms of over 6 weeks' duration, in the absence of other identifiable causes [1]. In the last decade, its definition changed significantly, especially after the exclusion of cystoscopic abnormalities as necessary findings for diagnosis [2, 3]. This occurred because, although some patients showed signs of inflammation on cystoscopy, the old definition was restrictive and encompassed only one third of patients with a presumptive diagnosis of BPS [4]. In addition, the lack of correlation between clinical findings and the degree of bladder inflammation described on bladder histopathology [5] encouraged the replacement of the classic term "interstitial cystitis" for BPS [2, 6].

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This condition primarily affects women around 40–60 years old, with varying prevalence [7]. In the USA, approximately 3–8 million women and 2 million men have BPS, which corresponds to prevalence rates of 2.7–6.5% and 1.9% respectively [7, 8]. In addition to disease-defining symptoms, affected individuals are prone to presenting stress, sleep disturbances, depression, and sexual dysfunction, with a significant quality of life (QoL) burden, more commonly than the general population [9–11] Such QoL effects are aggravated by the diagnostic delay, often of years, from symptom onset to appropriate diagnosis [11]. Yet, there is no specific, effective treatment for BPS. Despite the wide range of available therapies, evidence for the efficacy of each of them is limited by heterogeneous study methods, symptom evaluation tools, and duration of treatment or follow-up [1, 11].

Moreover, despite its individual and socioeconomic burden [12], the etiology of BPS remains unknown. Several hypotheses have been proposed, including urothelial dysfunction, immunological alterations, mastocyte changes, neurogenic causes, and urothelial growth inhibition by antiproliferative factor (APF); however, none of them remarkably proved the mechanisms of disease genesis, progression or resolution [13–16]. In light of this, its diagnosis has so far been based on the exclusion of other conditions that have similar clinical presentations, which can be challenging. Tools to facilitate its accurate diagnosis and objective follow-up are lacking and, so far, biomarkers clinically useful for such purposes are still under investigation [16].

Previous reviews have attempted to summarize the current knowledge on such biomarkers, but were limited as they had no limitations as to the diagnostic criteria included, thus limiting the interpretation of its results; did not use a systematic approach to collect and present their data, having great bias; or included patients with lower urinary tract symptoms, not BPS specifically [16–20].

Considering this, and especially considering the recent changes in the definition of this disease, an update on the current knowledge of this issue is needed. Thus, we conducted a systematic review to investigate possible biomarkers for the diagnosis and symptom evaluation of patients with BPS, defined according to the current criteria published by the American Urological Association (AUA) and the International Continence Society (ICS) [1, 2].

Materials and methods

Search strategy

The electronic databases Cochrane Library, PubMed/MEDLINE, Embase, LILACS, SCOPUS, and ClinicalTrials.gov were systematically searched for records published up to 27 October 2018. In each database, advanced searches were performed using "bladder pain syndrome" OR "interstitial cystitis" (including its synonyms or MeSH equivalents), AND "biomarkers" (including variants and MeSH equivalents). Specific keywords used in each database are shown in Supplementary Materials 1 through 6. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed [21]. Methods, definitions, and units conform to the standards jointly recommended by the International Urogynecological Association and the International Continence Society [22], except where specifically noted.

Eligibility criteria

We considered eligible observational (cross-sectional, case–control, and cohort) or experimental (if baseline data were presented) studies investigating biomarkers for the diagnosis and/or symptom assessment of patients with BPS defined as an unpleasant sensation (pain, pressure, or discomfort), related to the bladder, in the presence of lower urinary tract symptoms, over 6 weeks' duration, in the absence of other identifiable causes, which corresponds to the current AUA criteria [1] and encompasses the criteria reported by the International Continence Society (ICS) [2]. Only original research, peer-reviewed studies, were included. No restrictions to language of publication were applied. Animal or post-mortem studies, in addition to case reports, reviews, and studies using other criteria for the diagnosis of BPS, were excluded.

The reference lists of the articles included were used as additional sources for potentially eligible studies that could have been missed when searching databases.

Study selection

Title and abstract were screened for eligibility (primary screening) by two authors independently (TM and JH); discrepancies were solved by a third reviewer (EB). Full-text versions of papers were then obtained, and the same investigators independently screened them for inclusion in the final review (secondary screening).

Data extraction

Relevant data on each article were extracted using a standardized table. The variables evaluated were biomarker name, body tissue or fluid from where it was obtained, measures of diagnostic accuracy (sensitivity, specificity, and/or area under the curve [AUC]), techniques used for analysis, symptom assessment, and tool used for assessing symptoms.

Ethical concerns

Ethics committee approval does not apply to this type of research.

Results

Initial database search retrieved 861 records; after removal of duplicates, 478 records remained. Of these, 324 were excluded after primary screening and another 143 were excluded after secondary screening, resulting in the inclusion of 11 articles in the final review (Fig. 1). The exclusion of records using older criteria for the diagnosis of BPS largely contributed to the final total of only 11 articles.

Owing to heterogeneity and selective reporting within studies, risk of bias could not be assessed. As there was no more than one study on the same type of sample and biomarker, a quantitative analysis (meta-analysis) was not performed.

Most studies were observational and cross-sectional (Table 1). Sample sizes ranged from 16 to 198 participants. Seven articles analyzed solely women [23–28], whereas only 1 included male participants [29], and another 1 did not report subjects' gender [30]. In the remainder, both male and female participants were included [31–33].

Several methods were used for detecting biomarkers, most commonly immunoassay techniques such as radioimmunoassay (RIA), enzymatic immunoassay (EIA), and enzyme-linked immunosorbent assay (ELISA) [23, 25, 26, 28–32]. Techniques used in each study are described in Table 1.

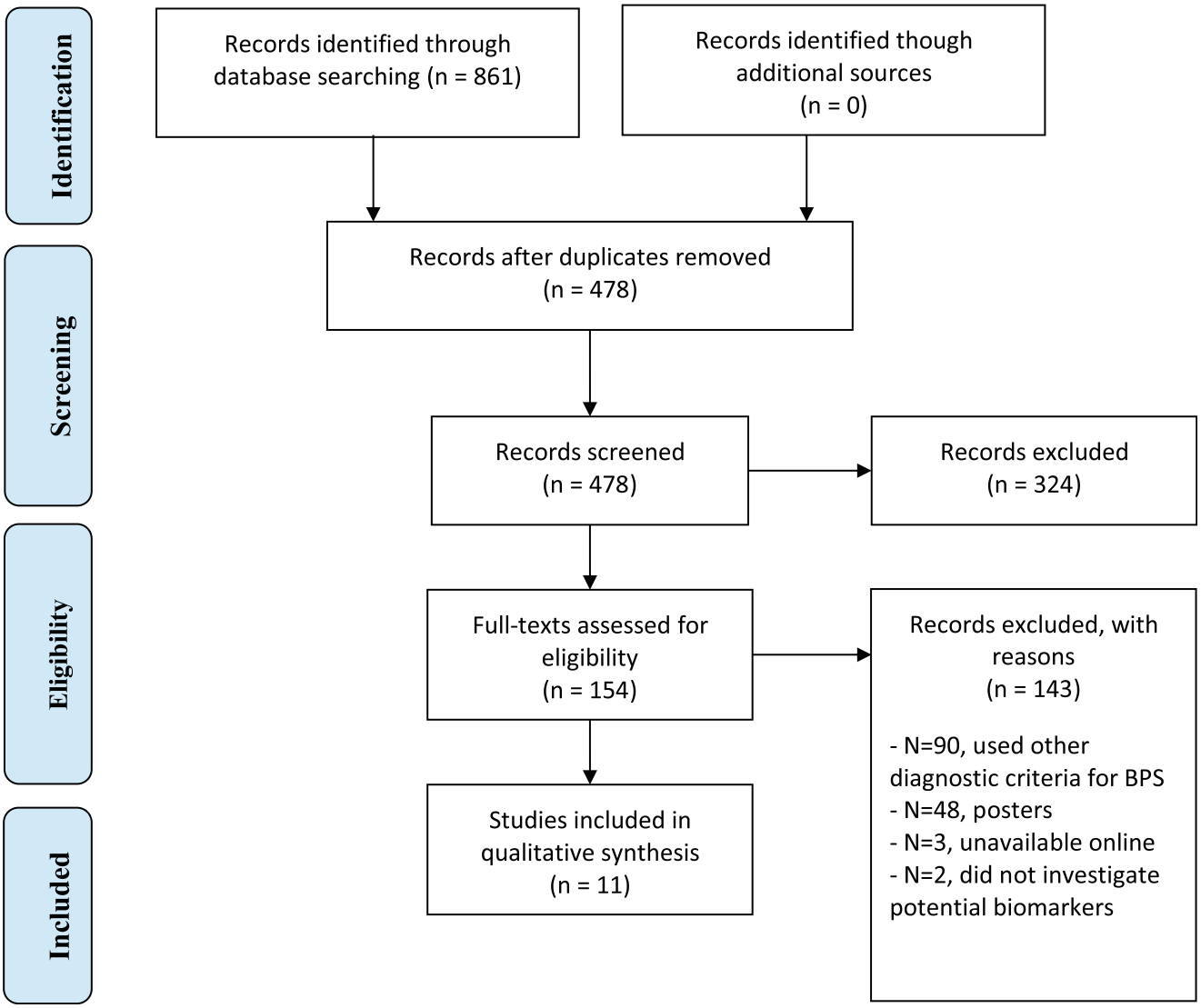

Fig. 1 Study selection flowchart

Table 1 Properties of the biomarkers investigated in each study. References are shown in chronological order, from the most to the least recent. Subjects' gender was specified whenever this information was reported in the original articles. Findings in the BPS column refer to patients with BPS in comparison with control groups, whereas findings in the Hunner column refer to patients with BPS and Hunner lesions in comparison with patients with BPS without Hunner lesions

Reference	Type of study	Subjects (final sample)	Biomarker	Source	Type of analysis	Findings				Relationship with symptoms
						BPS		Hunner lesions		
						Increased/ upregulated	Decreased/ downregulated	Increased/ upregulated	Decreased/ downregulated	
Bradley et al. [26]	Cross-sectional	8 patients with BPS 8 asymptomatic controls	DNA methylation analysis (differentially methylated CpG sites)	Urine	Quantitative DNA methylation assessment	–	MAPK pathway	–	–	NI. All cases had ICSI >8
Choi et al. [33]	Cross-sectional	25 men and women with BPS 5 controls	Expression of sonic hedgehog, WNT gene family, inflammation (CCR2, MCP-1, NF-kB), growth factors (HB-EGF, NGF), nitric oxide synthase (nNOS, iNOS, eNOS), and apoptosis (ARF) genes	Bladder biopsy	RQ-PCR, IHC, Western blot	ARF CHAT eNOS GLI-1 iNOS MCP-1 NGF WNT-10A WNT-8A	CHT HB-EGF OCT-1 SMRT-1 WNT11	ARF CCR2 CHAT CHT eNOS GLI-1 HB-EGF iNOS SMRT-1 WNT10A WNT2B WNT5A	–	NI
Vera et al. [28]	Cross-sectional	55 women with BPS without Hunner lesions 43 women with BPS with Hunner lesions 100 female controls	MIF	Urine	ELISA	MIF MIF/Cr	–	MIF MIF/Cr	–	NI
Shahid et al. [27]	Cross-sectional	10 women with BPS 10 female controls	ARID1A expression	Bladder biopsy	IHC	ARID1A	–	–	–	NI
Tonyali et al. [32]	Prospective cohort	15 women with BPS 18 male and female controls	NGF	Urine	ELISA	NGF/Cr	–	–	–	Correlated with OSICSPI score
		15 women with BPS 9 controls	Peripheral nerve twigs	Bladder biopsy	S-100 IHC	Mucosal nerve density	–	–	–	Correlated with OSICSPI score
Parker et al. [25]	Prospective cohort	40 women with BPS 40 female controls	Etio-S	Urine	LC-MS based metabolomics	Etio-S	–	–	–	G2 profile had worse pain and symptom scores than G1 (SYM-Q, GUPI, BPI, and AUASI).
Braundmeier-Fleming et al. [24]	Cross-sectional	18 women with BPS 16 female controls	Stool microbiome	Stool	Amplified sequencing, PCR, GC-MS based metabolomics	Glyceraldehyde	*Collinsella aerofaciens* *Eggerthella sinensis*	–	–	Phyla Actinobacteria, Firmicutes, and Proteobacteria

Table 1 (continued)

Reference	Type of study	Subjects (final sample)	Biomarker	Source	Type of analysis	Findings				Relationship with symptoms
						BPS		Hunner lesions		
						Increased/ upregulated	Decreased/ downregulated	Increased/ upregulated	Decreased/ downregulated	
							Faecalibacterium prausnitzii *Odoribacter splanchnicus*			selected based on GUPI symptom scores
Corcoran et al. [31]	Prospective cohort	10 men and women with BPS 10 male and female controls	Cytokine profile (23 types)	Bladder biopsy	Immuno-assay	CTACK E29 ICAM-1 IL-16 IL-18 MCP-3 SCGFβ TRAIL VCAM-1	–	–	–	NI
				Urine		–	MCP-3			MCSF, MCP-3, SDF1α: linear correlation with symptom improvement after hydrodistension
Lamale et al. [23]	Cross-sectional	40 women with BPS 29 female controls	Methyl-histamine, histamine, IL-6	Urine	RIA, ELISA	Histamine IL-6 Methylhistamine+ histamine model	–	–	–	NI
Keay et al. [29]	Prospective cohort	24 men with BPS 36 male controls	APF HB-EGF EGF	Urine	3H-thimidine incorporation in cell cultures ELISA	APF	HB-EGF	–	–	NI
Byrne et al. [30]	Cross-sectional	36 patients with BPS 23 controls	Glycoprotein G5P1	Urine	ELISA	–	G5P1/Cr	–	–	NI

APF antiproliferative factor, *AUAS1A* AT-rich interactive domain-containing protein 1A, *AUASI* American Urological Association Symptom Index, *AUC* area under curve, *BPI* Brief Pain Inventory, *BPS* bladder pain syndrome, *Cr* creatinine, *EGF* epidermal growth factor, *ELISA* enzyme-linked immunosorbent assay, *Etio-S* etiocholan-3alfa-ol-17-one, *GC* gas chromatography, *GUPI* Genitourinary Pain Index, *HB-EGF* heparin-binding epidermal growth factor-like growth factor, *IHC* immunohistochemistry, *IL-6* interleukin-6, *IL-16* interleukin-16, *IL-18* interleukin-18, *LC* liquid chromatography, *MAPK* mitogen-activated protein kinase pathway, *MIF* macrophage inhibitory factor, *MS* mass spectrometry, *NGF* nerve growth factor, *NI* not investigated, *OSICSPI* O'Leary-Sant Interstitial Cystitis Symptom and Problem Index, *PCR* polymerase chain reaction, *PUF* Pain, Urgency and Frequency Questionnaire, *RIA* radioimmunoassay, *SYM-Q* Symptom and Health Care Utilization Questionnaire

Potential biomarkers analyzed

Nerve growth factor (NGF) [28, 29] and heparin-binding epidermal growth factor-like growth factor (HB-EGF) [25, 29] were studied in two different records, however, deriving from a different source (urine or bladder mucosa). For all other biomarkers there was no more than one study each (Table 1).

In bladder biopsy samples, several genes (including WNT inflammation, growth factors, and apoptosis-related) [33] and AT-rich interactive domain-containing protein 1A (ARID1A) expression [27], peripheral nerve twigs [32], and chemokine profiles [31] were assessed.

The potential biomarkers investigated in urine specimens were macrophage inhibitory factor (MIF), nerve growth factor (NGF), etiocholan-3alpha-ol-17-one (Etio-S), methylhistamine, histamine, interleukin-6 (IL-6), APF, epithelial growth factor (EGF), HB-EGF, glycoprotein G5P1, and a chemokine profile, in addition to a DNA methylation analysis.

Stool microbiome [24] was also investigated as a potential source of biomarkers for BPS. No other body fluids or tissues were analyzed.

Bladder biomarkers

In one study, bladder tissue samples were 100% positive for ARID1A expression in 10 patients with BPS, whereas none of the controls showed positivity [27]. Moreover, BPS patients had downregulated WNT11 expression compared with controls [33].

In another piece of research, nerve density was significantly increased in cases relative to controls [32].

Corcoran et al. [31] determined the profile of 23 chemokines in 10 patients with BPS and 10 asymptomatic controls. Bladder tissue of patients with BPS showed significantly more IL-16, IL-18a, SCGFβ, CTACK, TRAIL, ICAM-1, MCP-3, and VCAM-1 than controls. After multivariate analysis, only IL-16, VCAM-1, and ICAM-1 could differentiate the two groups.

Urine biomarkers

Tonyali et al. [32] simultaneously determined urinary NGF in addition to nerve density in the bladder mucosa. Similar to nerve density, urinary NGF/Cr was significantly increased in cases relative to controls in their study.

Also, assessing both urine and bladder biopsy samples, Corcoran et al. [31] determined 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 PBS from controls.

Bradley et al. [26] aimed to determine DNA methylation profiles in 8 women with BPS and 8 age- and race-matched controls. No genome scale significantly different methylation in CpG sites was found after Bonferroni correction. In the most significantly differentially methylated CpG sites from regression models, the pathway most prominently enriched was the mitogen-activated protein kinase pathway (MAPK). This pathway had 86% of its sites hypomethylated in the BPS group compared with controls.

Using liquid chromatography-MS in urine samples of 40 women with BPS and 40 controls, principal component analysis by Parker et al. demonstrated there to be two distinct metabolomic profiles in women with BPS [25]. The first (G1) had a profile similar to controls, which was distinct from the metabolomic profile of the second (G2). To determine exactly which metabolites and classes of metabolites could distinguish patients in subgroup G2 from the others, the authors used graphic representations and found six metabolites most closely associated with 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 two BPS 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 BPS, with 91.2% sensibility, 87.4% specificity, and 0.92 AUC. In the longitudinal analysis of women in this cohort, differences in Etio-S persisted, showing that these changes are long-lasting.

Vera et al. [28] investigated urinary MIF concentrations in controls and in subgroups of BPS with and without Hunner lesions. They verified that urinary MIF and MIF/Cr ratio was significantly higher in the Hunner lesion subgroup compared with patients without Hunner and with controls. Between the latter two, no differences in urinary concentrations of these factors were observed. Moreover, receiver-operator characteristics (ROC) analysis showed that the optimal urinary MIF cutoff value to differentiate BPS patients with and without Hunner lesions would be 109.4 pg MIF/mL, at which sensitivity was 74.4%, specificity 71.8%, and AUC 0.718. For the urinary MIF/Cr ratio, the optimal cutoff value of 3,659 pg MIF/mg Cr had 47% sensitivity, 91% specificity., and 0.730 AUC in identifying patients with BPS and Hunner lesions.

In turn, Lamale et al. [23] investigated urinary histamine, IL-6, and methylhistamine in women with and without BPS. Those with BPS had increased urinary concentrations of histamine (AUC 0.644) and IL-6 (AUC 0.731), but no significant differences were observed in methylhistamine levels. Logistic regression analysis demonstrated that the best predictor for BPS was a combined model with IL-6 and methylhistamine, with an AUC of 0.788. 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.

Moreover, Keay et al. [29] analyzed urine specimens of 24 men with BPS and 36 asymptomatic controls. Cases had significantly more APF activity than controls, but decreased HB-EGF concentrations. Groups had similar EGF levels. Furthermore, Byrne et al. [30] demonstrated that glycoprotein G5P1 concentration in urine specimens was lower in BPS than in controls.

Stool biomarkers

Finally, Braundmeier-Fleming et al. [24] studied the stool microbiome of 18 women with BPS and 16 controls. Patients with BPS had significantly reduced levels of *Collinsella aerofaciens*, *Eggerthella sinensis*, *Faecalibacterium prausunitzii*, and *Odoribacter splanchnicus*, with AUC in ROC analysis of 0.86, 0.84, 0.79, and 0.72 respectively. Stool metabolomics identified glyceraldehyde as significantly increased in the BPS group (AUC 0.98).

Symptom assessment

Only 4 studies analyzed the relationship between biomarkers and symptoms presented by patients (Table 1). Symptom assessment was done through one of six questionnaires: the American Urological Association Symptom Index (AUASI), the Brief Pain Inventory (BPI), the Genitourinary Pain Index (GUPI), the O'Leary-Sant Interstitial Cystitis Symptom and Problem Index (OSICSPI), the Pain, Urgency, and Frequency Questionnaire (PUF), and the Symptom and Health Care Utilization Questionnaire (SYM-Q).

Tonyali et al. [32] demonstrated that urinary NGF/Cr ratio significantly correlated with scores of both OSICSPI domains. Likewise, nerve density also correlated with both domains of this questionnaire. Despite this, NGF/Cr and nerve density were not correlated.

In Parker et al. [25], BPS patients in subgroup G2 had significantly worse pain and symptom scores, as assessed using the SYM-Q, GUPI, BPI, and AUASI tools.

Corcoran et al. [31] investigated correlations between symptoms and urinary chemokine profile. The following proteins showed significant, linear correlation with symptom improvement after hydrodistention, in the PUF questionnaire: MCSF ($r = 0.88$), MCP-3 ($r = 0.81$), and SDF1α ($r = 0.82$). However, when pre-hydrodistention levels were analyzed, none of the proteins correlated with symptom scores.

Finally, in stool microbiome, extended random forest (ERF) analysis identified operational taxonomic units that were associated with GUPI symptom scores at the phylum level, namely Actinobacteria, Firmicutes, and Proteobacteria [24].

Discussion

This systematic review showed that several potential biomarkers have been investigated in BPS patients; however, only a small number of studies used the diagnostic criteria of the AUA and ICS in the patient selection process (Fig. 1). The wide variety of criteria precludes study comparisons, which, in turn, hampers the synthesis of current evidence on biomarkers and their role in disease etiology, in addition to the development of effective therapies for BPS.

Macrophage inhibitory factor is constitutively expressed in human urothelial cells [28]. In rodent models, MIF is stored in the urothelium and released into the vesical lumen after vesical insults, then binds to receptors in the bladder surface and mediates bladder pain and inflammation [34, 35]. MIF had previously been shown to be increased in other bladder diseases, such as bacterial and radiation cystitis, which potentially reduces its specificity in the differential diagnosis of bladder pain [28, 36].

In addition, further reports suggest that MIF might release NGF, a factor that was also increased in samples from patients with BPS [32]. Studies showed increased NGF in the urothelium of patients with painful conditions of the urinary bladder [37, 38].

The increased ARID1A expression in BPS subjects [27] is thought to be due to DNA hypomethylation caused by alpha-oxoglutarate, which inhibits cell–cycle transitions in bladder epithelial cells [27] and could potentially cause bladder wall abnormalities. This is consistent with the finding of thinner epithelial layers in BPS patients [39, 40], as is the finding of low urinary glycoprotein G5P1 levels in BPS subjects [30]. The physiological role of ARID1A in maintaining hemostasis of the bladder epithelium by controlling chromatin remodeling [41] is another mechanism that could explain its relationship to disease pathogenesis. Furthermore, downregulation of WNT11 expression, reported in patients with BPS, has previously been associated with bladder tissue fibrosis, suggesting yet another possible mechanism for BPS symptoms.

Etio-S is a sulfoconjugated 5-beta reduced isomer of testosterone. High local concentrations of Etio-S can stimulate acute phase reactions. Etio-S could also act as a positive allosteric modulator of the GABA-A receptor [42], which is ubiquitous in the central nervous system and could explain some of the findings in BPS. This, along with its great association with the significantly symptomatic BPS group, suggests that it might play a part in disease processing, although the notion that it might be a consequence of BPS pathogenesis cannot be ruled out [43].

The high cytokine levels described in BPS by Corcoran et al. [31] reinforce the possible role of inflammation in disease symptoms. Interestingly, urinary protein levels did not correlate with BPS symptoms before hydrodistention, suggesting that hydrodistention might facilitate the identification of biomarkers in urine, perhaps by exposing bladder wall proteins closer to its surface. Although that study had the advantage of investigating the association of such potential biomarkers with patients' symptoms, its results were limited by the small sample size. Lamale et al. [23] developed a combined model of two metabolites that showed good accuracy in distinguishing BPS and controls. However, no analysis was performed on its relationship with symptoms or on its levels over time (longitudinal analysis), weakening its potential as a biomarker.

The MAPK pathway mentioned by Bradley et al. [26] is associated with cell growth inhibition, inflammation, and mediation of apoptosis. Its association with the pathophysiology of BPS is unclear, but could be related to the inhibition of normal cell growth and cell turn-over. However, further studies are needed to show if the reduced methylation of MAPK pathways in BPS has functional repercussions.

Braundmeier-Fleming et al. [24] suggested that gastrointestinal changes might contribute to symptomatology in urological pain syndromes. Among the significant bacteria mentioned, *F. prausnitzii* is highlighted as a source of butyrate, whose deficiency is associated with irritable bowel syndrome, another painful condition [44]. In individuals with BPS certain foods frequently trigger symptoms [45]; as such, spontaneous dietary modifications adopted by BPS patients could have affected the results of this study. Finally, Keay et al. [29], in addition to reporting significant differences in HB-EGF and APF levels in men with and without BPS, also described significant differences in men with BPS and chronic prostatitis. This result reinforces the theory that, despite being clinically similar, such conditions could have different pathophysiological mechanisms [46].

Although promising, the clinical relevance of such biomarkers is not clearly established. The results presented here provide clues to pathophysiological mechanisms in BPS and important information for the design of future studies. For a BPS biomarker to be implemented into clinical practice, findings would have to be replicated in BPS subgroups with several clinical presentations and prospective validation studies would have to be performed. Moreover, further work should investigate the relationship between biomarkers and BPS symptoms using validated questionnaires, to enable future comparisons between studies, in addition to changes in biomarker levels in response to treatment and symptom improvement.

The strengths of this review consist of the strict inclusion criteria, evaluating only those studies with patients who fulfill current AUA and ICS criteria for BPS. We also included in our search strategy the three largest electronic databases in this subarea. Weaknesses primarily involve the low yield of articles included and the inability to proceed with a meta-analysis as it was not possible to pool results. Another flaw is the inclusion of articles evaluating BPS in both men and women. In BPS, disease mechanisms may differ according to gender, similar to other lower urinary tract diseases [47–49]; however, we opted to include studies in men in addition to women in view of the limited number of articles available for inclusion. We suggest that future studies on BPS might be developed, specifically investigating the female population, to achieve results more relevant to this population.

Conclusion

This systematic review concluded that urinary MIF, NGF, Etio-S, APF, and methylhistamine/IL-6 were increased in BPS samples compared with controls; similar results were shown for fecal glyceraldehyde and for bladder epithelial expression of some genes (ARID1A, ARF, CHAT, eNOS, GLI-1, iNOS, MCP-1, NGF, WNT-8A, WNT-10A), nerve density, IL-16, VCAM-1, and ICAM-1. In contrast, urinary DNA methylation in CpG sites, MCP-3, glycoprotein G5P1, and HB-EGF levels, in addition to a few bacterial species in stool and CHT, HB-EGF, OCT-1, SMRT-1, and WNT11 expression were reduced in BPS samples.

The only potential biomarkers that were investigated against symptoms were fecal bacterial flora, urinary metabolomic profiling, urinary NGF/Cr levels, urinary cytokine profile, and bladder mucosa nerve density. In all the relevant studies, validated questionnaires were used for this purpose.

Several substances obtained from urine, feces or bladder biopsy specimens have been investigated as potential biomarkers for BPS. Further research is needed before they can be used in clinical practice.

Compliance with ethical standards

Conflicts of interest None.

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