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VOIDING DYSFUNCTION EVALUATION (B BRUCKER AND B PEYRONNET, SECTION EDITORS)

Urinary Biomarkers and Benign Prostatic Hyperplasia

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Abstract

Purpose of Review Benign prostatic hyperplasia (BPH) is a common age-related benign proliferation of the epithelial and stromal components of the prostate. Symptomatic BPH is associated with the progressive development of lower urinary tract symptoms (LUTS), which left untreated can deteriorate over time and lead to acute urinary retention, urinary incontinence, recurrent urinary tract infections, and/or obstructive uropathy.

Recent Findings Surgical or medical treatment that correct bladder outlet obstruction from BPH in patients generally resolves voiding symptoms and reduces the urine levels of neurotrophins. Histological analysis of the prostate biopsies obtained from BPH patients enrolled in large clinical studies supported the role of prostatic inflammation in BPH/LUTS. However, the invasive nature of biopsy motivates the research in alternative biofluids for the discovery of biomarkers to influence the clinical management of BPH. We recently reported that urinary levels of chemokines are associated with the evidence of prostatic inflammation and measures of obesity in BPH patients.

Summary Detection of inflammatory mediators in urine of BPH patients has the potential to displace biopsy for discriminating BPH-related pathologies, identify risk of progressive disease, and personalize the management of BPH-related LUTS.

Keywords Urine · BPH · Prostatic inflammation and chemokines

Introduction

Several large epidemiological studies implicate benign prostatic hyperplasia (BPH) as a metabolic disorder, whose prevalence generally increases with increasing age [1•]. Clinically, BPH can be classified as either symptomatic or asymptomatic BPH [2•]. Diagnosis of symptomatic BPH is primarily based on a diverse array of progressive lower urinary tract symptoms (LUTS) secondary to benign enlargement of the prostate gland and ensuing bladder outlet obstruction. In contrast, asymptomatic BPH is a histologic diagnosis, which is characterized by non-malignant proliferation of the epithelial and stromal components of the prostate in absence of LUTS.

LUTS of symptomatic BPH patients is broadly grouped into storage (urgency, frequency, nocturia) and voiding symptoms characterized by a sensation of not completely emptying the bladder, stop-start urination, straining to urinate, a need to urinate soon after voiding, and a weak urinary stream [2•]. It is generally believed that prostate enlargement is the possible cause of bladder outlet obstruction to urine flow, which ultimately leads to LUTS [3•]. However, a large body of evidence from controlled clinical studies supports the absence of a linear relationship between prostate enlargement and the severity of LUTS [4••, 5]. Median score of American Urological Association-symptom index (AUA-SI) in the measurement of LUTS was higher in cancer-free BPH patients with median prostate volume of 32.5 mL enrolled in Medical Therapy of Prostatic Symptoms (MTOPS) studies [5] than in the cancer-free BPH patients enrolled in the Reduction by Dutasteride (0.5 mg) of Prostate Cancer Events (REDUCE) study [4••] with median prostate volume of 44.4 mL. Other studies have also shown that men with significantly enlarged prostates often do not present with LUTS, while some men with normal size of prostate [6•] experience severe LUTS. Moreover, surgical or medical treatment targeted towards the obstruction of enlarged prostate relives the voiding symptoms much earlier than storage symptoms [7••].

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Although BPH/LUTS is generally not life-threatening, it does significantly impact the quality of life (QoL) in patients and its societal treatment costs are more than $4 billion annually [8]. For decades, the core of BPH research has centered on androgen signaling, which leads to the development of 5-alpha reductase inhibitors (5ARI), such as finasteride and dutasteride. Although prostate biopsy is currently an accepted standard to investigate pathophysiological mechanisms associated with BPH, an earlier study found that transition zone prostate biopsy correctly predicted the histology of the whole prostatectomy specimens in only 20% of prostate cancer cases [9]. Therefore, biopsy method is highly sensitive to site selection bias and the risk-benefit ratio of biopsy for cancer-negative BPH patients is very high. Typically, BPH patients with enlarged prostate consent for biopsy and prostatectomy, but pathogenetic mechanisms deciphered from the study of larger prostate cannot be extrapolated to BPH patients with smaller prostate as gene expression changes drastically with the prostate size [10, 11].

Existing medical treatment paradigm for BPH of α-adrenergic blockers (α-blockers) to relax muscle tone and 5ARI to shrink the prostate ignores the complexity of size-dependent gene expression in prostate. Moreover, treatment response to 5-ARI is dependent on prostate size [12•] and treatment failure results in around 120,000 surgical interventions annually in the USA [13]. LUTS, if left untreated, can result in acute urinary retention, urinary incontinence, recurrent urinary tract infections, and/or obstructive uropathy [14], so there is a need for new non-invasive methods to distinguish the etiology of BPH/LUTS symptoms and thus inform the treatment decision making.

MTOPS Prostatic Samples Analysis (MPSA) Consortium and other groups are pursuing the discovery of serum biomarkers to discriminate BPH-related pathologies. Although blood levels of prostate-specific antigen (PSA) are associated with BPH, poor specificity of PSA for BPH is ill-suited for discriminating mild from severe BPH/LUTS [13, 15] and information on the treatment options. Autocrine/paracrine communication mediated by chemokines and growth factors is essential for the normal organogenesis as well as benign and malignant prostatic growth [16, 17]. The analysis of chemokines and other inflammatory mediators in biofluids is therefore preferable as a matrix for biomarker discovery for BPH. Chemokine levels in urine are shown to be associated with pathological changes in prostate and bladder [18–20]. Urine is an appealing non-invasive matrix for BPH biomarkers [21, 22••, 23•, 24, 25•] as it contains vesicles directly derived from the prostate. Hence, dynamic changes in urine in response to prostatic inflammation makes it a reliable source for searching non-invasive biomarkers of BPH phenotypes to identify risk of progressive disease and personalize the clinical management of BPH-related LUTS [26•, 27•].

BPH and Bladder Outlet Obstruction

BPH often leads to bladder outlet obstruction (BOO), which is characterized by compression of prostatic urethra preventing the urine outflow from bladder [28]. BOO initially provokes compensatory bladder wall remodeling [29], which, in the absence of proper treatment, can lead to deterioration of the bladder over time. In some cases, this can lead to detrusor underactivity (DU), defined as a contraction of reduced strength and/or duration leading to incomplete bladder emptying [30•]. Initial compensatory changes are evident as bladder wall hypertrophy increased intravesical pressure, which can increase the transient episodes of hypoxia and ischemia in the bladder wall [29]. Hypoxic and ischemic episodes in the bladder wall elicit upregulation of angiogenic factors, muscarinic receptors, and neurotrophins including nerve growth factor (NGF) and Brain-derived neurotrophic factor (BDNF) [29]. Higher expression of NGF and BDNF in the bladder has been studied in association with LUTS in clinical [23•] and animal studies [31•]. NGF overexpression in the bladder is considered to sensitize bladder afferents, which leads to the storage symptoms in BPH/LUTS and leads to NGF elevation in urine of obstructed patients [32•]. Urine levels of BDNF also correlated with the severity of LUTS in BPH patients [23•]. Androgen deprivation is the most prominent medical therapy targeted towards obstruction in BPH patients [12•] and relief from obstruction in Dutasteride-treated BPH patients was associated with reduced urine levels of NGF. Surgical castration was shown to increase prostaglandin expression in bladder urothelium of male rats [33•], which may explain the delay in the resolution of storage symptoms relative to the voiding symptoms in dutasteride-treated BPH patients [34]. Molecular changes in the bladder wall of BPH patients demonstrate that the bladder is not an innocent bystander to benign prostatic enlargement.

Prostatic Inflammation and BPH

Healthy prostate is an immunocompetent organ, populated with a small number of stromal and intraepithelial T and B lymphocytes [35]. Intraprostatic lymphocytic infiltration in the prostate tissue is a sign of inflammation [36], which is phenotyped by grade, extent [37], and the density of CD3+ and CD20+ staining [25•]. Inflammatory infiltrates in BPH prostate are mainly represented by $CD3^+$ T lymphocytes (70–80%) or CD20 B lymphocytes (10–15%) [11, 38]. Studies report that frequencies of $CD3^+$ cells are increased at least tenfold in the hyperplastic tissues [39] and the lower prevalence of $CD20^+$ B lymphocytes supports B cell activity as a late event in BPH progression [11, 38]. Intraprostatic infiltration in the transition zone of prostate [11] was positively associated with the LUTS scores [11], but inflammation in peripheral zone is not strongly associated with LUTS [40••].

Histological analysis of prostate biopsy tissue removed from symptomatic BPH patients in large clinical studies including MTOPS and REDUCE men identified prostatic inflammation as a major predictor for unfavorable outcomes in placebo-treated BPH patients [4••, 41]. A 4-year longitudinal evaluation of placebo-treated BPH patients in REDUCE trial confirmed that histologic signature of chronic inflammation is associated with the severity and the progression of BPH/LUTS [4••, 42–44]. A large Olmsted county study on BPH patients found that daily use of non-steroidal anti-inflammatory drug (NSAID) was inversely associated with the onset of moderate/severe urinary symptoms [45].

Prostatic Inflammation and Chemokines

Numerous stromal and epithelial factors have been implicated in the etiology of BPH/LUTS including androgens, chemokines, and growth factors [8]. Chemokines are secreted by a variety of cells, including leukocytes, epithelial cells, endothelial cells, smooth muscle cells, and numerous other cells [46]. Constitutive expression [47] of chemokines, neurotrophins, and growth factors by stromal fibroblasts and prostate epithelium [48, 49] is critical for maintaining the homeostasis in prostatic microenvironment [46]. Since inducible expression of chemokines temporally precedes the intraprostatic infiltration of immune cells [50], chemokines are often designated as molecular signatures of prostatic inflammation [36]. In fact, measurement of chemokines in prostate tissue, in expressed prostatic secretions, and in serum have been used as an index of prostatic inflammation [14, 51, 52].

Chemokines belong to a family of small secreted glycoproteins with molecular weight of 7–10 KDa with over 50 ligands [53]. Structurally, chemokines are subdivided into two major families (CC and CXC), where CC class is distinguished by adjacent position of the first two cysteines (e.g., CCL2 and CCL5) and CXC chemokines contain an intervening amino acid(s) between the first two conserved cysteine residues. CXC chemokines [48, 54] are produced in the epithelium of the lower urinary tract after induction IFN-γ [55]. Higher serum levels of CXCL-5 in BPH compared to non-diseased individuals [56] is linked to the higher secretion of CXCL-5 by stromal fibroblasts obtained from BPH patients with histological evidence of infiltration [54]. An earlier study from our group performed microarray analysis of prostate tissue from organ donors and patients with histological and symptomatic BPH undergoing surgery for either prostate or bladder cancer. Symptomatic BPH patients with prostate gland size in the range of 30–193 g showed upregulated expression of CXCR4 receptor (binds to CXC chemokine CXC12) relative to histological BPH patients [57]. Recent studies suggest CXC chemokines, which are disproportionately elevated in urine relative to serum are likely to mediate the myofibroblast phenoconversion for the promotion of fibrotic changes in prostate tissue [58].

CC chemokines namely CCL5 and CCL3 are known to be chemotactic for the infiltration of $CD3^+$ T lymphocytes and CD20 B lymphocytes, respectively [13]. Therefore, elevated levels of CXCL-1, CXCL-8, CXCL-10, CCL2, CCL3, and CCL5 in prostate tissue and in biofluids of symptomatic and asymptomatic BPH patients [59, 26•, 60, 13, 56, 19, 61, 48] imply chemoattraction of CD3+ and CD20+ lymphocytes into the prostate. The measurement of multiple inflammatory mediators implies that the initiation and perpetuation of prostatic inflammation are mediated by the complex interplay of multiple factors, rather than the isolated effects of single signaling molecules or pathways [16].

Urine Biomarkers of BPH

BPH biomarker discovery and translation remain a challenging task and various matrices including prostate tissue, serum, urine [22••], seminal plasma, and prostatic secretions have been analyzed for identifying diagnostic and prognostic biomarkers. MPSA Consortium seeks to develop a molecular understanding of the BPH with serum-based diagnostic and prognostic biomarkers of BPH [14]. The biomarker discovery template followed by MPSA Consortium is that BPH biomarkers should be first identified in prostate and subsequently detected and analyzed in serum [14]. Elevated serum PSA levels were found to be associated with prostatic inflammation of BPH in one study [62] but the findings have not been reproducible [15, 63] and may reflect the presence of prostate cancer.

Compared to serum, urine collected non-invasively by the patient [64] himself has obvious advantages as a suitable matrix for BPH biomarker discovery. Proteomic composition of urine is constituted by proteins filtered by the kidney from blood or directly secreted by the upper and lower urinary tract [65]. 100-fold higher levels of PSA [66] and chemokines like CCL2 in urine [67] over respective serum levels suggests preferential excretion of proteins from the prostate into urine [68] (Fig. 1) by utilizing the anatomic continuity of prostate with urethra [65]. Large molecular weight of PSA is consistent with a direct secretion from prostate into urine instead of increased excretion of a 26 kDa protein [69] from BPH patients with normal kidney function tests. Prostate cancer is excluded from BPH patients enrolled in urine biomarkers study, either by serum PSA levels or by absence of malignancy in the prostate biopsy taken before urine collection.

As discussed in the subsequent sections, urine biomarker discovery is biased towards detecting proteins that are overexpressed in the lower urinary tract, such as PSA [66], neurotrophins, and sIL-1RA. Successful response to removal of the bladder outlet obstruction by transurethral resection of

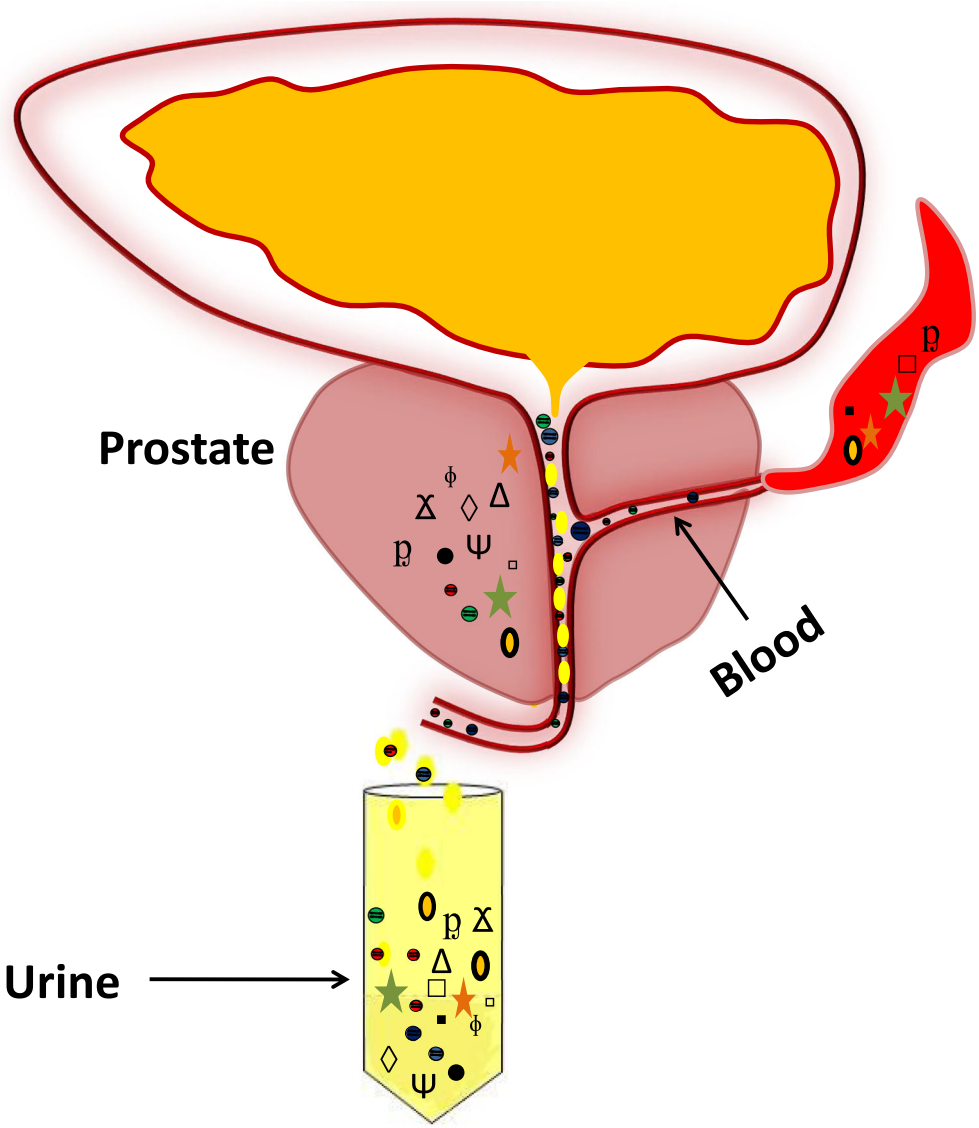

Fig. 1 Schematic illustration for the abundance of prostatic proteins in urine—anatomic continuity of prostate with urethra facilitates the preferential drainage of PSA and overexpressed CXC chemokines via shedding and budding of micro and multivesicular bodies from prostate. Median urine levels of CXC chemokines, CXCL-1, CXCL-8 [67], and CXCL-10 [35] in BPH patients are higher than the reported serum levels of respective chemokines in BPH patients [42]. Analysis of rat urine found very high levels of IFN-γ (◊), CXC chemokines except CXCL-5 (•), interleukins except IL-5, and growth factors (ϕ). Excess production of CC chemokines CCL5 (□) and CCL3 (Δ) by the inflamed rat prostate was shed into urine. Relative abundance in urine with concomitant absence in serum for EGF, GM-CSF, IFN-γ, IL-1β, IL-10, IL-18, and eotaxin in serum suggest direct contribution from prostate to urine. Preferential secretion of IL-1α, IL-2, IL-4, IL-6, IL-13, IL-17A, VEGF, leptin, CCL2, and CXC chemokines (CXCL-1, CXCL-2,CXCL-5, CXCL-10) into urine from inflammated prostate is supported by rat study

prostate (i.e., TURP) was associated with reduction of NGF levels in urine of BPH patients [21, 70]. Dutasteride treatment in obstructed BPH patients produced similar results in urine NGF levels [70]. A separate study on medical therapy of BPH/LUTS patients found that urine levels of the microRNA, miR-21-5p level were an independent predictor of response to phosphodiesterase 5 inhibition by tadalafil in multivariate regression analysis [24].

Stromal enlargement is the predominant histologic feature of BPH/LUTS and chemokines primarily produced in stroma (CCL2) [19, 60] and in prostatic epithelium (CCL5, CXCL-10) [48, 61] are potential candidates for assessing the prostatic inflammation. CCL2 was easily detectable in normally voided urine specimens (without prostate massage) from ~ 90% of enrolled patients of our study [25•, 59]. Studies published from other groups also found elevated expression of CCL2 in prostatic fluids of BPH [18, 19], which suggest that higher tissue expression of CCL2 and PSA [66] in prostate leads to their elevation in urine [25•, 59]. In contrast to the elevated urine levels of PSA and CCL2 in BPH patients, low and undetectable levels of IL-6 in urine of BPH/LUTS patients [25•] suggest relatively lower tissue expression of IL-6 in the prostate. This premise is supported by the significant association of chemokine levels in urine and the chemokine levels measured in respective bladder punch biopsy of interstitial cystitis patients [71]. Therefore, differences in urine levels of CCL2 and IL-6 in BPH patients [13, 59] is consistent with the reported 40-fold difference in the serum levels of CCL2 and IL-6 [56].

Unlike CCL2, comparison of the CCL5 levels in the urine of BPH patients [59] with the thousand-fold higher serum levels of CCL5 in BPH patients of another study [56] implicates that CCL5 is not preferentially secreted from the enlarged prostate into urine. Urine levels of CXC chemokines (CXCL1, CXCL2, and CXCL10) were dominant over their

respective serum levels reported from another study on BPH patients [56]. The levels of CXCL-10, CCL3, and CCL5 in normally voided urine specimens of healthy male asymptomatic control subjects are much lower than those reported for BPH patients [26•, 72]. This comparison of urine levels of chemokines from one study with serum levels reported from another study justifies the need for studying a direct relationship between urine and serum levels of BPH-associated proteins.

Urine or serum measurement of inflammatory proteins [73, 74] may be relevant in measuring the molecular differences underlying clinical (symptomatic) vs histological (asymptomatic) BPH. This will require simultaneous measurement of inflammatory proteins in biofluids and the density of $CD3^+$ and CD20+ lymphocytic infiltration in prostate biopsy of BPH patients. Within each image of the bladder biopsy, regions of inflammation (ROI) which included confluent sheets of inflammatory cells, with or without tissue destruction or lymphoid nodule or follicle formation were identified as reported earlier [75]. The extent of inflammation was calculated as the total area of all ROI across all images for that patient divided by the total tissue area scored for that patient × 100, to yield as the percent of all analyzed cores for a given patient with inflammation. A three-tiered grading system proposed by Nickel and colleagues [37] estimated the inflammatory cell density in each ROI as mild, moderate, and severe.

In our study, BPH patients with greater intensity of CD3+ and CD20+ lymphocytic infiltration in the prostate biopsy cores showed greater elevation of CXCL-10, CCL5 and CCL3 in urine [25•]. Elevation of CXCL-10 in urine was marginally associated with the extent of inflammation, and CCL3 was marginally associated with the grade of inflammation in biopsy cores [25•]. CCL3 was also found elevated in seminal plasma levels of BPH patients [52], which taken together with urinary elevation of CCL3 in BPH patients [25•] suggests its preferential secretion of CCL3 into urine from prostate. Association of CCL3 with the moderate grade of inflammation in BPH patients suggest co-existence of prostatitis and BPH in some patients as CCL3 levels were detected in prostatic fluids of prostatitis patients [20]. The association of different chemokines with the pathological metrics of inflammation in prostate biopsy suggests that different chemokines regulate different facets of inflammation.

Simultaneous multiplex analysis of inflammatory proteins in serum and urine specimens obtained from rat model of prostatic inflammation [76] (Fig.1) found that majority of the prostatic inflammation-associated proteins were readily detected in urine samples, while they were undetectable in serum [77]. Relative abundance of EGF, GM-CSF, IFN-γ, IL-1β, IL-10, IL-18, and eotaxin in urine with their concomitant absence in rat serum suggest that direct contribution from prostate led to the elevation in urine. Species-wise differences in the urine output may explain the measurable amounts of CCL11 (eotaxin −1) and IL-1β in the serum of BPH patients relative to non-diseased individuals [56, 78•]. It is likely that these proteins including VEGF are directly derived from the prostate and other urological organs via direct shedding and budding of vesicles containing these proteins from the plasma membrane [65]. The findings imply that urinary elevation of inflammatory mediators associated with prostatic inflammation can happen independently of their serum elevation. Simultaneous analysis of chemokines in serum and urine of women also reported discordance between two biofluids [79].

Obesity and BPH

A role of metabolic stress in the pathogenesis of BPH [80] and prostatic inflammation is suggested by different epidemiological studies and by the higher prevalence of BPH/LUTS in obese subjects [78, 81]. A key determinant of metabolic syndrome is the increased centralized deposition of adipose tissue, which is also one of the predisposing factors for BPH. Our urine analysis of obese BPH patients found a broad and robust relationship between a key measure of centralized fat deposition, which is a waist-hip ratio, and increased urine levels of soluble interleukin receptor antagonist, sIL-1Ra [25•, 59]. Elevated urine levels of sIL-1RA also showed association with other measures of obesity including body mass index and waist circumference in patients of incidental BPH with mild to moderate LUTS [59].

sIL-1RA was first detected in urine three decades ago, a 22–26-kD anti-inflammatory cytokine which regulates the signaling of IL-1α and IL-β by binding to their cognate receptors without inducing any response [82]. The anti-inflammatory effect of sIL-1RA in prostate stromal cells was shown earlier, where it blocked the epithelium-mediated induction of chemokine expression in primary stromal cells [83]. It is of interest that the genes for human IL-1Ra gene (IL1RN) and the cytokines IL-1α and IL-β are mapped to the band q14-q21 in the long arm of chromosome 2, with a separation of only 300 base pairs [82, 84, 85]. Therefore, monocytes, macrophages, neutrophils, epithelium, hepatocytes, and adipocytes after expressing IL-1α and IL-β also express sIL-1RA in tenfold higher amounts to negatively regulate the IL-1 signaling [82]. In the absence of inflammation, serum levels of sIL-1RA are maintained by constitutive secretion of sIL-1RA from hepatocytes [86]. The expression of sIL-1RA in adipocytes is induced by leptin, and serum leptin levels showed a significant association with prostate enlargement and greater body size of BPH patients [78•]. Therefore, higher leptin levels in serum portends higher urine levels of sIL-1RA in obese BPH patients [78•].

Expression and function of IL-1α in driving the enlargement of transition zone of prostate [87, 88] has been extensively studied, but the urine levels of IL-1α are rarely above the detection limits in BPH patients [64, 26•]. Presumed tenfold higher expression of sIL-1RA in the prostatic tissue can explain the copious presence of sIL-1RA in urine together with relative absence of IL-1α and IL-β in urine. Strong association of urinary sIL-1Ra with obesity measures of waist-hip ratio, waist circumference, and body mass index (BMI) of BPH patients and the elevation of sIL-1Ra in the serum of morbidly obese men [89] implicates that sIL-1Ra is the key molecular correlate of obesity in BPH pathogenesis [89, 90]. Gene polymorphism in sIL-1Ra has also been studied in relation to BPH risk in patients [84].

Comparable magnitude in the median urine levels of sIL-1Ra for overweight BPH patients and serum sIL-1Ra levels in lean men [89, 90], suggests that serum elevation of sIL-1Ra likely precedes the elevation of sIL-1Ra in urine. Cross-sectional studies are ill-suited to explore the temporal relationships between outcomes and so simultaneous longitudinal measurement of serum and urine specimens from same BPH patients are necessary to investigate a temporal relationship between the elevation of sIL-1Ra in serum and in urine. A direct comparison between adipokine levels in biofluids of symptomatic BPH and age-matched asymptomatic healthy patients can shed light on their relationship with LUTS. Since recombinant analogue of sIL-1Ra (Anakinra) is FDA approved for treating auto-immune disease of rheumatoid arthritis [91], urine levels of sIL-1Ra can serve as treatment biomarker for treating prostatic inflammation in BPH patients with Anakinra.

Perspectives

An ideal biomarker should be easily assayed with minimally invasive medical procedures but possess high sensitivity and specificity. Although many candidate biomarkers have been proposed in the literature, very few have made their way to clinical use. Prostate biopsy as a matrix for biomarker discovery is sensitive to sampling error and false negatives [92]. Blood is a body fluid of high complexity, which has been traditionally preferred in search of biomarkers [14]. However, blood does not capture all the inflammatory chemokines released from the inflamed prostate [77] and the low specificity of serum PSA for prostate cancer can mean many unnecessary prostate biopsies [22••]. So, a urinary marker based on metabolomics [22••] or chemokines or neurotransmitters for BPH [59, 93] is likely to mirror the inflammatory state of prostate without the site selection bias of biopsy and the inflammation induced by the biopsy procedure. Instead of traditional immunoassays detecting single protein in urine, multiplex assays offer the promise of simultaneously evaluating many proteins, leading to the possibility of identifying novel biomarkers that would otherwise be overlooked by individual immunoassays. Urine metabolomics could be an alternative approach for understanding the biological pathways relevant in BPH/LUTS. A recent study found higher levels of glycine, dimethylglycine, fumarate, and 4-imidazole-acetate, and lower levels of branched-chain amino acids including glutamate and pseudouridine in BPH relative to prostate cancer patients [22••].

Preferential drainage from prostate into urine may explain the relatively higher median urine levels of CXC chemokines, CXCL-1, CXCL-8 [94], and CXCL-10 [48] in BPH patients compared to the reported serum levels of respective chemokines in BPH patients [56]. Higher levels of prostatic proteins in normally voided urine compared to serum is premised on direct excretion from the prostate [20, 66, 95–98], lower dilution of chemokines secreted into urine compared to those taken up in serum (~ 200 mL in single urine void vs ~ 5-L-average blood volume) [99], and relatively lower levels of proteases in urine relative to serum [100]. Several reports indicate a rise in serum levels of proteases following inflammatory disease [101]. The continuous scale of chemokine levels in urine can improve the objective classification of BPH patients and overcome the constraints of binary outcome based on detection of inflammation in prostate biopsy [102]. Recent studies demonstrate that urine is an easy to collect, information-rich biofluid that can provide surrogate markers for concurrent monitoring of prostatitis, interstitial cystitis (IC), and BPH [64, 103, 104]. However, there is paucity of information on the prognostic value of responses to each BPH treatment for all the BPH biomarkers described so far. Indeed, such data will be paramount to move these biomarkers from bench to bedside.

Conclusions

Chemokines detectable in urine could potentially fill void of non-invasive biomarkers for BPH that are suitable for real-time detection and application to the management of BPH patients. Identification of urine biomarkers that can assist with risk-stratification of BPH patients would be of considerable benefit, as their use will identify risk of progressive disease and personalize the management of BPH-related LUTS.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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