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Promising Molecular Targets and Biomarkers for Male BPH and LUTS

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Abstract

Benign prostatic hyperplasia (BPH) is a major health concern for aging men. BPH is associated with urinary voiding dysfunction and lower urinary tract symptoms (LUTS), which negatively affects quality of life. Surgical resection and medical approaches have proven effective for improving urinary flow and relieving LUTS, but are not effective for all men and can produce adverse effects that require termination of the therapeutic regimen. Thus, there is a need to explore other therapeutic targets to treat BPH/LUTS. Complicating the treatment of BPH/LUTS is the lack of biomarkers to effectively identify pathobiologies contributing to BPH/LUTS or to gauge successful response to therapy. This review will briefly discuss current knowledge and will highlight new studies that illuminate the pathobiologies contributing to BPH/LUTS; potential new therapeutic strategies for successfully treating BPH/LUTS; and new approaches for better defining these pathobiologies and response to therapeutics through the development of biomarkers and phenotyping strategies.

Keywords

Benign Prostate Hyperplasia; Biomarkers; Collagen; Fibrosis; Inflammation; Lower Urinary Tract Symptoms; Molecular Targets; Myofibroblast; Novel Therapeutic Intervention

Introduction

Benign prostatic hyperplasia (BPH) is a chronic, progressive disease of the prostate which affects more than 30% of men aged 60 or older and results in a significantly negative impact on quality of life [1]. This negative impact is due to various co-morbidities that develop concurrently with BPH, that lead to lower urinary tract symptoms (LUTS). As recently reviewed by McVary (2007), LUTS is itself a progressive disorder that is manifest as urgency, nocturia, urinary frequency, weak urinary stream, and incomplete bladder emptying. Without effective treatment, LUTS can lead to bladder outlet obstruction and subsequent bladder wall hypertrophy, increased bladder mass, and bladder dysfunction manifest as acute urinary retention, recurrent urinary tract infections, bladder stones and, eventually, renal dysfunction [1].

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Current clinical management for BPH/LUTS includes surgical ablation and medical approaches using anti-androgens or smooth-muscle relaxers. Surgical ablation, though effective, may provide only a temporary measure for relief as prostate tissue continues to proliferate and obstruct urethral function. Medical therapies for male BPH/LUTS include 5 α -reductase inhibitors, which repress androgen-mediated prostate growth, and α 1-adrenergic receptor antagonists, which relieve voiding difficulty by relaxing smooth muscle in and around the prostate and bladder. Though effective for many men, these therapeutics are not effective for all men and can produce adverse effects that require termination of the therapeutic regimen. Moreover, the use of such therapeutics, singly or in combination, decreases but does not abrogate the risk for disease progression [2]. This suggests that additional, potentially therapeutically targetable, biological processes may also contribute to BPH/LUTS.

The identification and implementation of efficacious treatment strategies to alleviate BPH/LUTS is further confounded by a lack of useful biomarkers to identify specific contributing pathobiologies or response to targeted therapeutics. Although urinary voiding dysfunction due to bladder dysfunction can be assessed using urodynamics and other objective tests, dysfunction due to prostate pathobiology is often assessed using self-reported means. For more than twenty years, male LUTS has been assessed using the self-reported American Urological Association Symptom Index (AUASI) [3]. The AUASI uses a 0-5 scale to indicate frequency of symptoms, with 0=none and 5=almost always, across 5 categories: Completeness of bladder emptying, urinary frequency, intermittent stream, urgency, weak stream, straining, and nocturia. Scores of 0-7 suggest absent or mild symptoms; 8-19, moderate symptoms; and 20-35, severe symptoms. Subsequent to its initial adoption, a separate Quality of Life (QOL) category was added, also rated on a scale of 0-6, with 0=delighted and 6=terrible, to indicate the general level of unhappiness and bother associated with the level of reported LUTS [4]. Though useful, assessment of BPH/LUTS using AUASI scores is a subjective and imprecise method for gauging disease extent, etiology, prognosis, or therapeutic response. Clearly, a more contemporary approach, such as metabolic phenotyping, would be useful for a precise assessment of disease biology and personalized therapeutic strategy [5].

This review will briefly discuss current knowledge regarding the pathobiology of BPH/LUTS, targeted therapeutic strategies, and biomarker development. The focus of this review, however, is to highlight new studies that illuminate the pathobiologies contributing to BPH/LUTS; potential new therapeutic strategies for successfully treating BPH/LUTS; and new approaches for better defining these pathobiologies and response to therapeutics through the development of biomarkers and phenotyping strategies.

Targeted Therapeutic Strategies for the Treatment of BPH/LUTS

I. 5 α -Reductase Inhibitors

A. Finasteride and Proscar—Prostate growth and function is regulated by steroid hormones, particular androgens. The androgen receptor, AR, is a member of the nuclear steroid hormone receptor superfamily and mediates androgen-dependent gene transcription [6]. After the active form of testosterone, dihydrotestosterone (DHT), binds to AR in the cytoplasm, the AR/DHT complex translocates to the nucleus and activates many genes that encode proteins required for prostate growth [7]. Prostate growth is regulated by the balance between cell proliferation and cell death. Since AR is a major driver of prostate cell growth and survival, current therapeutic approaches to treat BPH/LUTS are aimed at inhibiting androgen hormone production and/or blocking AR signaling. Accordingly, drugs like 5 α -reductase inhibitors, including finasteride (Proscar) and dutasteride (Avodart), block

the conversion testosterone to its active form, DHT, and are widely used for BPH/LUTS therapy [8-9] (Table 1).

B. Phytotherapeutic agents—Phytotherapy, or the use of plants and herbs for medicinal purposes, has been popular for the treatment of BPH/LUTS for many years [10-11]. The use of phytotherapeutic agents in the US has significantly increased, with a recent survey reporting that one-third of American men choosing non-surgical therapy for BPH were using herbal preparations alone or combined with prescription medications [12].

Ginseng—A recent study showed that red ginseng represses androgen-promoted prostate hyperplasia by blocking AR signaling [10•]. Ginseng is known to have various pharmacological activities. Recent in vivo data indicated that water extract of Korean red ginseng (WKRG) prevented prostate overgrowth and epithelial thickening induced by testosterone in rats, and suppressed the production of rat prostate-specific antigen (kallikrein-S3) by repressing AR signaling [13]. In human prostate cells, WKRG inhibited testosterone-induced cell proliferation, induced cell cycle arrest and apoptosis, repressed expression of human kallikrein-3 mRNA, and inhibited AR activation [10•]. In addition, one of the major ginsenosides of WKRG, 20(S)-Rg3, suppressed AR activity and inhibited androgen-mediated prostate cell growth by enhancing degradation of the AR protein. Since red ginseng has been used safely in Asia for many years, red ginseng and 20(S)-Rg3 could be potential therapeutic agents for treating BPH [10•].

Saw Palmetto—American saw palmetto (*Serenoa repens*) is an over-the-counter phytotherapeutic agent used to self-treat BPH/LUTS. Recent high quality, long-term clinical trials reported that *Serenoa repens* therapy was no better than placebo in reducing LUTS in men with BPH. One 12-month trial that enrolled 225 patients reported that *Serenoa repens* therapy did not improve symptoms or urinary flow [14]. A study reported in 2011 designed as a, dose-escalation trial (320, 640, and 960 mg/day saw palmetto extract) with 72 weeks follow-up indicated that the effect of *Serenoa repens* on alleviation of LUTS was no better than placebo at 24, 48, and 72 weeks, respectively [15]. Another study reported in 2012 echoed this finding and showed that treatment with *Serenoa repens* extracts, even at escalating doses, did not improve LUTS or QOL associated with BPH [16].

Permixon® (Pierre Fabre Medicament, Castres, France), a lipido-sterolic extract of *Serenoa repens*, has been extensively studied for the treatment of LUTS/BPH [17-18]. Permixon combination with α 1-adrenergic receptor blockers is associated with benefits in terms of speed of onset of action, reduction of inflammation, and a positive benefit regarding sexual problems when compared with use of α -blocker alone [19].

Isoflavones—Two forms of isoflavones, aglycone and glucoside, are mainly used as dietary supplements among patients with BPH [20]. These are polyphonic compounds found in soy food and red clover. Several studies have shown that isoflavones reduce the proliferation of glandular epithelium in the prostate by blocking 5 α -reductase activity and inhibiting 17-phydroxysteroid dehydrogenase and aromatase activity [21]. Numerous studies also linked a low incidence of BPH with a diet rich in isoflavones, e.g., Japanese men with a low incidence of BPH exhibited high levels plasma and urine isoflavone phytoestrogens [22]. Moreover, the risk for developing BPH and prostatic cancer increased significantly for men migrating from low BPH incident countries to high incident counties and adopting local dietary [23].

II. α 1-Adrenergic Receptor Antagonists

α 1-adrenoceptor antagonists (α -blockers) have been used to alleviate LUTS by reducing prostatic smooth muscle tone. Based on pathophysiological models of male LUTS as well as numerous data on prostatic α 1-adrenoceptors indicated that α -blockers improve male LUTS by preventing prostatic smooth muscle contraction and reduce symptom of BPH/LUTS. During the past few years, α 1-adrenergic receptor blockers have been considered the most effective therapy for BPH/LUTS [24]. There are several α -blockers available include the quinazolines alfuzosin, doxazosin, terazosin and the non-quinazolines tamsulosin and, most recently, silodosin. Several studies have indicated that all α -blockers are similarly effective in treating LUTS when used in appropriate doses, but can differ quantitatively and their tolerability [25]. Tamsulosin (Flomax) was one of the most effective and well-tolerated α -blockers used for men with LUTS [26].

A. α 1-adrenergic receptor blockers and anticholinergic therapy—The LUTS spectrum can include bladder dysfunction primarily that associated with overactive bladder (OAB), which can be treated with anticholinergic agents [27]. Therefore, some treatment strategies have combined the use of α -adrenergic receptor blockers to target prostate and bladder smooth muscle contractility with anticholinergic therapy to target OAB. Numerous studies have shown that combination treatment with anticholinergic agents and α -blocker can improve LUTS in some men more effectively than either agent alone and does not increase the risk of voiding difficulty [28-30]. However, as for other treatment strategies, combined α -blocker and anticholinergic treatment does not resolve voiding difficulty for all men, with one study showing that 13% of men after 3 months combination treatment still reported voiding difficulty [31].

B. α 1-adrenergic receptor blockers and add-on fesoterodine therapy for LUTS/OAB—Antimuscarinics, with or without a α -blocker, may be effective for the treatment of OAB-associated storage symptoms in some men. Flexible-dose fesoterodine as an add-on treatment significantly improved urinary frequency and symptom bother, but not urgency episodes, versus placebo. Fesoterodine was well tolerated in men with persistent OAB [32].

C. The use of phosphodiesterase 5 inhibitors alone or in combination with α 1-adrenergic receptor blockers for BPH/LUTS—Phosphodiesterase (PDE) enzymes are involved in the regulation of the nitric oxide-cyclic guanosine monophosphate (cGMP)-protein kinase pathway and mediate smooth muscle relaxation. PDE5 inhibitors (PDE5-Is) lead to increased nitric oxide level in smooth muscle, allowing penile erection and prostate and bladder neck relaxation [33]. An impaired cGMP signaling seems to be involved in the pathophysiology of BPH, suggesting that PDE5-Is may have a role in the management of LUTS [34-35]. Studies on different PDE5-Is have demonstrated an improvement in LUTS/erectile dysfunction in men with both conditions, without increase in adverse events [36]. Therefore, combination of PDE5-Is and α 1-adrenergic receptor blockers may have an additive favorable effect on BPH/LUTS.

A recent study conducted a systematic review and meta-analysis of available prospective and cross-sectional studies on the use of PDE5-Is alone or in combination with α 1-adrenergic receptor blockers in patients with BPH/LUTS. The combined findings of this study supported a role for PDE5-Is therapy for successful treatment of LUTS and erectile dysfunction in men with BPH [37••]

III. Desmopressin

Nocturia is described as the need to wake to void once or more per night [38]. It is considered clinically significant when >2 nightly episodes are experienced, can have a

profound negative effect on QOL, and, due to concomitant impaired sleep, can have profound negative effects on work productivity, cognitive performance, mood, and mortality [39-40]. Treatment approaches include self-management via fluid restriction and medical therapies for BPH/LUTS. However, while these may be effective for daytime BPH symptoms, may not effective for nocturia [41]. The majority of patients with nocturia have nocturnal polyuria, which is associated with decreased nocturnal secretion of arginine vasopressin (AVP) hormone [42].

Desmopressin acetate, a synthetic analog of AVP, mimics the action of the AVP hormone, and desmopressin tablets have been shown to be tolerated and effective treatment for nocturia in adults with nocturnal polyuria in clinical trials [43-45]. Desmopressin has most recently been formulated as an orally disintegrating tablet which is administered sublingually without water. It is an effective and a well- tolerated treatment for nocturia. It prolongs the first sleep period and thereby improves patients' QOL [46].

IV. Role of a Self-Management Intervention for BPH

Conservative management for BPH is called watchful waiting or active monitoring and can vary from checkup visits to a urologic service to an intensive program of education, and advice delivered in a multidisciplinary setting. Some men with LUTS receive specific lifestyle and behavioral advice to give them some control over their symptoms such as: fluid management, caffeine avoidance or bladder retraining to enhance an effect on the urinary tract [47••]. Many of the interventions mentioned above require time and dedication from physicians, the program facilitator and the patient. In addition, it is important to realize that the adverse impact on QOL from some of the interventions, e.g., changes in caffeine and alcohol consumption may be significant enough to make them infeasible. Changing patients' behavior and maintaining these changes is not an easy task [47••].

A recent study indicated that self-management intervention is associated with decreased LUTS symptoms and may improve QOL in BPH patients receiving α 1-adrenergic receptor blockers [47••]. The use of lifestyle and behavioral interventions in the form of a self-management program may not only those normally managed with watchful waiting, but also as a primary treatment strategy for all men with LUTS. If self-management fails, medical or surgical intervention is required.

V. Fibrosis a Novel Therapeutic Target for BPH/LUTS Treatment

Fibrosis is defined by the excessive proliferation of fibroblasts and myofibroblast and the excessive accumulation of collagen and other extracellular matrix (ECM) components in and around inflamed or damaged tissue, which can lead to permanent scarring and organ dysfunction.

Fibrogenesis is becoming increasingly recognized as a major cause of morbidity and mortality in many chronic inflammatory diseases, such as idiopathic pulmonary fibrosis (IPF), non-alcoholic fatty liver disease [48-56]. In vivo studies using mouse models have biologically linked obesity-induced diabetes and inflammation with lower urinary tract fibrosis and urinary voiding dysfunction [54••]. Chronic inflammation has been noted in the prostate in the context of prostatitis and histological inflammatory infiltrate [57-58]. Prostatitis is a common condition that accounts for about 2 million ambulatory care visits annually in the United States. Several studies have indicated an association between chronic prostatic inflammation and development of LUTS [59-60]. In addition, chronic inflammation has been noted in several histological studies of the prostate [61-64]. Previous studies from our laboratory showed that elevated collagen content, higher levels of inflammation, higher levels of fibrocytes (progenitor cells that can differentiate into

myofibroblasts), increased tissue stiffness, reduced levels of elastin, reduced glandularity characterizes the peri-urethral prostate tissues of men experiencing moderate/severe LUTS compared to men who do not reported LUTS [55••]. This suggests that fibrosis is a previously unrecognized pathobiology contributing to LUTS. These studies also showed that peri-urethral tissues from the prostates of men experiencing LUTS express significantly higher levels of CXC-type chemokine receptors compared to men without LUTS [56••]. Therefore, some patients with LUTS may benefit from antifibrotic treatment alone or in combination with the currently prescribed regimen of 5 α -reductase inhibitors and/or α 1-adrenergic receptor antagonists. Prostate fibrosis and major pathobiological processes that can act alone or in combination to promote male LUTS shown in Figure 1.

Pro-Fibrotic Factors in the Prostate

TGF β 1: TGF β 1 is a multifunctional cytokine with broad regulatory activities such as regulation of cell proliferation and migration, carcinogenesis, wound healing, inflammation and fibrosis among others [65-66••]. It is secreted by smooth muscle cells, infiltrating immune cells and carcinoma-associated fibroblasts in the prostate [67-69]. TGF β 1 promotes fibrosis by driving fibroblast to myofibroblast phenoconversion, epithelial-mesenchymal transition (EMT), and ECM deposition [64]. TGF β 1 also contributes to fibrosis by inhibiting ECM degradation by downregulating expression of matrix metalloproteases (MMPs), plasminogen activators, as well as enhancing the expression of tissue inhibitors of metalloproteases (TIMPs) and plasminogen-activator inhibitors (PAIs) [70-73]. Upregulation of TGF β 1 correlates with the progression of lung, heart, liver, and renal fibrosis, and inhibition of the TGF β 1 signaling pathway has been shown to attenuate the development of fibrosis in animal models [74-76]. Recently the roles of TGF β 1 in fibrosis have been reviewed [49, 66]. The central roles of TGF β 1 and its inhibitors in prostate fibrosis and LUTS are shown in Figure 1.

CXC-Type Chemokines: CXC-type chemokines are a family of small (~10kD) secreted proteins that share a similar structure comprising two conserved cysteines separated by one unconserved amino acid. There are several members of the CXC-type chemokine family with both conserved and diverse functions, though all CXC-type chemokines signal through membrane-bound G-protein coupled receptors (GPCRs) [77]. Several studies have shown that CXC-type chemokines are up-regulated and secreted by aging prostate stromal fibroblasts, potentially due to the acquisition of a senescent phenotype by increasing numbers of fibroblasts experiencing low-level DNA damage through replicative exhaustion or cumulative oxidative (or other) stresses [78]. Senescent fibroblasts express a senescence-associated secretory profile that includes over-expression and secretion of a medley of CXC-type chemokines (CXCL1, CXCL2, CXCL3, CXCL8, and CXCL12) [79], similar to that over-expressed and secreted by aging human prostate stromal fibroblasts [79].

Peri-urethral tissues from the prostates of men experiencing moderate/severe LUTS express significantly higher levels of CXCR4, the receptor for CXCL12, compared to men without LUTS [56••]. Moreover, primary prostate stromal fibroblasts morphologically undergo myofibroblast phenoconversion and express the fibrosis-associated transcripts and proteins, such as collagen I and α -smooth muscle actin, when exposed to the CXCL-type chemokines CXCL5, CXCL8, or CXCL12 [56••]. The central roles of CXC-type chemokines and chemokine receptor antagonist in prostate fibrosis and LUTS are shown in Figure 1.

Fibrosis as a New Therapeutic Target for BPH/LUTS Managements

The studies cited above suggest that fibrosis may comprise a new therapeutic target for the treatment of BPH/LUTS, especially for men who do not respond to, cannot tolerate, or become refractory to current of 5 α -reductase inhibitor- and/or α -1 adrenergic-receptor

antagonist- based therapies [80]. A number of studies have shown that inhibition of TGF β or CXCR4 prevents the development of fibrosis [49-51, 56, 66, 75, 80-87].

TGF β 1 Antagonists—Given the central role of TGF β 1 in fibrosis, drugs targeting TGF β 1 may be efficacious for the treatment of fibrosis. Therapeutic approaches include strategies to block TGF β 1 at the receptor level with monoclonal antibodies or receptor tyrosine kinase inhibitors, as well as those intended to block pro-fibrotic signaling pathways downstream of receptor activation. Several large- and small-molecule drugs inhibiting TGF β 1 are being tested in preclinical and clinical trials patient with fibrotic diseases. The therapeutic agents most studied include Pirfenidone, an anti-TGF β 1 that inhibits fibroblast proliferation; GC1008, an antibody that neutralizes TGF β 1 ; IFN- γ 1b, a TGF β 1 antagonist that inhibits fibroblast differentiation; anti- α v β 6 neutralizing antibodies that block TGF β 1; Resveratrol that inhibits TGF β 1 and decreases proliferation and collagen synthesis; SD-208, a small-molecule TGF β 1 receptor kinase inhibitor, and Gleevec, a protein kinase inhibitor with activities against tyrosine kinases and PDGF [49-51, 66, 75, 80-85]. Major TGF β 1 inhibitory drugs that are currently being developed primarily to treat fibrotic disease are summarized in Table 2.

CXCR4 Antagonists—Fibrocytes rapidly enter the sites of tissue injury, and may contribute to scar formation. Recent findings suggest that CXCR4-positive fibrocytes may migrate into the IPF lungs, likely in response to stromal-derived factor-1 (SDF-1/CXCL12) a specific ligand for CXCR4 [86-87•]. A pathogenic role for fibrocytes in pulmonary fibrosis has been suggested in experimental models in which neutralization of CXCL12 or blockade of CXCR4, with a specific antagonist for CXCR4, AMD3100 results in reduced recruitment of fibrocytes to the injured lung and attenuation of fibrosis [86-87•]. Recent studies show that CXCL12/CXCR4 axis activation promotes myofibroblast phenonversion in the prostate, which can be inhibited by treatment with AMD3100 [56••]. Taken together, these studies suggest that interfering with chemokine/chemokine receptor interactions may diminish myofibroblast recruitment and accumulation and repress fibrosis

Biomarkers for BPH/LUTS Detection

As noted earlier in this Review, the identification and implementation of efficacious treatment strategies to alleviate BPH/LUTS is complicated by the lack of useful biomarkers to identify specific contributing pathobiologies or response to targeted therapeutics. The current practice of using AUASI scores to clinically diagnose BPH/LUTS and gauge treatment efficacy is flawed by the subjectivity and imprecision of self-reported symptomology. Clearly, a more contemporary approach, such as metabolic phenotyping, would be useful for a precise assessment of disease biology and personalized therapeutic strategy [88••]. Here we review the small number of biomarkers useful for the detection of BPH/LUTS, especially those useful for gauging clinical progression and/or therapeutic response.

I. Prostate-Specific Antigen (PSA)—Though typically regarded as a serum marker for prostate cancer, PSA is also a marker for BPH in the absence of cancer. Several studies have shown that serum PSA values increase concomitantly with patient age in parallel with increased incidence of BPH [89-91]. However, given the controversy surrounding the use of serum PSA for prostate cancer detection, it is unlikely that serum PSA values would demonstrate utility as a biomarker for BPH progression or therapeutic response [92-93].

II. CCL1 (I-309)—A study initially examining 12 inflammatory proteins – CC- and CXC-type chemokines as well as interleukins – as serum markers for prostate cancer identified one marker, CCL1 (I-309) that demonstrated elevated levels in association with BPH rather

than PCa [94]. CCL1 is a small (15-18 kdal) secreted glycoprotein and is the sole ligand for the G-protein coupled receptor, CCR8 [95]. CCL1 was also reported to be elevated in seminal plasmas from patients with BPH [96]. Although high levels of CCL1 protein have now been identified in both the serum and seminal fluid of men with enlarged prostates, the cellular source for CCL1 expression is likely activated T-cells in the prostate tissue microenvironment [97]. The CCR8 receptor is expressed on a variety of cell types including activated T-helper-2 (Th2) cells [98]. The T lymphocyte population in particular expands enormously in BPH/LUTS, increasing from a mean of 7 cells/mm² in the normal prostate to a mean of 195 cells/mm² in fully developed BPH [99]. Therefore, it is not surprising that a chemokine largely secreted by activated T-cells may be found at significantly elevated levels in the serum of men with enlarged prostates. Other studies have demonstrated that T-lymphocytes promoted the proliferation of both transformed and non-transformed prostate epithelial cell lines in vitro [100], suggesting that high serum levels of CCL1 may signify the presence of large T-lymphocyte populations in the prostate that, in turn, promote prostate tissue proliferation and prostatic enlargement.

Conclusions

Current clinical management strategies for BPH/LUTS includes surgical ablation and medical approaches using 5 α -reductase inhibitors and/or α 1-adrenergic receptor antagonists. Medical management may also include combination therapies with PDE5-I and/or antimuscarinics. There are also several phytotherapeutic agents, many available without prescription, which may provide symptom relief for some men. Clinical practice has shown that anti-androgens and smooth muscle relaxers used alone or in combination, are effective for many men though they do not prevent BPH/LUTS progression and may not provide durable symptom relief. This suggests that additional, potentially therapeutically targetable, biological processes may also contribute to BPH/LUTS. One such pathobiology, tissue fibrosis, may be therapeutically targetable through inhibition of TGF- β 1 or CXCL12-mediated intracellular pathways. However, the identification and implementation of efficacious treatment strategies to alleviate BPH/LUTS is complicated by the lack of useful biomarkers to identify specific contributing pathobiologies or response to targeted therapeutics. The current practice of using AUASI scores to clinically diagnose BPH/LUTS and gauge treatment efficacy is flawed by the subjectivity and imprecision of self-reported symptomology. Clearly, a more contemporary approach, such as metabolic phenotyping, would be useful for a precise assessment of BPH/LUTS disease biology and personalized therapeutic strategy.

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Figure 1. Male BPH/LUTS Pathogenic Mechanisms And Therapeutic Strategies

Lower Urinary Tract Symptoms can result from multiple pathobiologies, including aging; prostatic enlargement; lower urinary tract fibrosis; and lower urinary tract smooth muscle dysfunction. Over-arching pathobiologies, such as inflammation, may be exacerbated by the aging process and contribute to both prostatic enlargement and fibrosis. Components of particular pathobiologies may be therapeutically targetable. For example, prostatic enlargement arises from epithelial proliferation, which can be targeted by 5- α -reductase inhibitor and phytotherapeutics, and/or fibroblastic proliferation, which can be targeted by TGF- β 1 inhibitors. Similarly, fibrosis, arising from myofibroblast differentiation and consequent collagen and ECM production, can be targeted by TGF- β 1 inhibitors, TGF- β 1 receptor antagonists, and/or chemokine receptor antagonists. Smooth muscle dysfunction can be targeted by α -1-adrenergic receptor antagonists alone or in combination with anticholinergics, antimuscarinics, or PDE5 inhibitors. Response to therapeutics may be determined using pathobiology-specific biomarkers, such as Prostate Specific Antigen (PSA) or CCL1 for prostatic enlargement, or collagen I (COL1) for fibrosis.

Table 1**Major Therapeutic Agents for the Management of BPH/LUTS**

Classification	Agent	Mechanism of Action
5- α -Reductase Inhibitors	Proscar Avodart	Inhibits proliferation and reduces the size of the prostate
Phytotherapeutics	Red Ginseng, 20(S)-Rg3 Saw Palmetto Isoflavones	Blocks androgen receptor signaling.
α -1-Adrenergic Receptor Antagonists	<i>A1 selective inhibitors:</i> Alfuzosin Alfuzosin XL Prazosin Doxazosin Doxazosin GITS Terazosin	Inhibits α - adrenergic receptor activity and relieves voiding difficulty by relaxing smooth muscle around the prostate. Inhibits type α 1A, α 1B, α 1D receptors.
Arginine Vasopressin Analogs	Desmopressin acetate	Replenishes arginine vasopressin, relieves polyuria/nocturia.

Abbreviations: XL, extended-release; GITS, gastrointestinal therapeutic system

Table 2Major Anti-TGF β and CXCL12 Therapeutic Agents Used to Manage Fibrosis

Classification	Agent	Mechanism of Action
TGF- β 1 Inhibitors	Pirfenidone GC1008 IFN- γ lb α v β 6 Resveratrol	Inhibits fibroblast proliferation Inhibit TGF β 1, TGF β 2 and TGF β 3 TGF β antagonist, inhibit fibroblast differentiation Blocking antibody that blocks TGF β Decreases proliferation and collagen synthesis
TGF- β 1 Receptor Antagonists	Imatinib meylate (Gleevec) SD-208	Block both TGF β and PDGF receptors Inhibit TGF β RII kinase activity
Chemokine/Chemokine Receptor Inhibitors	AMD3100 DD-Nac-PGP	Targets CXCR4; Inhibits fibrocytes migration Targets CXCR2; Inhibits neutrophil recruitment in chronic inflammation and fibrosis