Submitted: 17 January, 2026 Accepted: 29 April, 2026 Published: 30 August, 2026 DOI:10.22514/jomh.2026.066

REVIEW

JOMH Journal of Men's Health

Inflammatory and immunomodulatory regulatory mechanisms in benign prostatic hyperplasia

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Abstract

Benign prostatic hyperplasia (BPH) is one of the most common urologic diseases, and its incidence continues to increase. Although its pathogenesis remains incompletely understood, accumulating evidence suggests that chronic inflammation is involved in the initiation and progression of BPH. Accordingly, BPH is increasingly regarded as an immune-inflammatory disease, and targeted anti-inflammatory therapy has emerged as a promising research direction. This review summarizes the role of chronic inflammation in BPH, focusing on immune cells, inflammatory mediators, nuclear factor kappa-B (NF-κB), the NOD-like receptor protein 3 (NLRP3) inflammasome, the T helper cell 17 (Th17)/Interleukin-17 (IL-17) axis, and other related signaling pathways in the prostate. It also discusses the interactions between inflammation, metabolic syndrome (MetS), and the gut microbiota, and reviews the current status of anti-inflammatory therapy for BPH, with the aim of providing a theoretical basis for targeted anti-inflammatory treatment.

Keywords

Benign prostatic hyperplasia; Pathogenesis; Inflammation; Immunomodulation

1. Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases of the male urinary system and is pathologically characterized by an increase in both glandular and stromal cell numbers within the transitional zone of the prostate and the periurethral region, ultimately resulting in prostate enlargement. Clinically, patients with BPH usually present initially with lower urinary tract symptoms (LUTS), including urinary frequency, urgency, and nocturia. As the disease progresses, complications such as urinary retention and even renal dysfunction may occur, substantially impairing quality of life. The global burden of BPH is substantial. According to the Global Burden of Disease (GBD) database, the worldwide disease burden attributable to BPH increased continuously from 1990 to 2017; by 2017, BPH accounted for 2,427,334 years lived with disability (YLDs)—nearly three times the burden of prostate cancer (PCa)—indicating that BPH has become a major health concern among aging men worldwide. With continued population aging and increasing life expectancy, this burden is expected to rise further [1].

The pathogenesis of BPH has not yet been fully elucidated. In addition to aging and alterations in androgen status, chronic inflammation has increasingly been recognized as a key contributor to disease initiation and progression. An autopsy study involving 320 patients with BPH showed that more than 70% of prostate specimens exhibited chronic inflammation [2]. Clinical cohort studies have further demonstrated that patients with histological inflammation have larger prostate volumes, a higher incidence of urinary retention, and higher International Prostate Symptom Score (IPSS) values [3]. Multiple stimuli, including infection, urinary reflux, metabolic syndrome, aging, and autoimmune responses, may disrupt immune homeostasis in the prostate, thereby promoting inflammatory-cell infiltration and the formation of a pro-inflammatory microenvironment [4]. Through the release of cytokines and growth factors, this process promotes cellular proliferation and drives inflammatory hyperplasia of prostatic tissue during repeated cycles of tissue injury and repair, thereby contributing to the development and progression of BPH [5]. Moreover, this process may also be involved in the development of rare prostatic disorders such as granulomatous prostatitis, as well as prostate cancer, thereby adversely affecting patient health [6].

In this context, inflammation is increasingly regarded as a critical link between local tissue alterations and systemic regulatory factors. This review summarizes the inflammatory features associated with BPH, with a particular focus on immune-cell infiltration, cytokine networks, and key signaling pathways. In addition, it discusses the regulatory roles of metabolic syndrome and the gut and urinary microbiota, as well as the potential clinical value of inflammation-related targets in the diagnosis and treatment of BPH.

2. Inflammatory phenotype of BPH tissue

2.1 Immune cells in chronic inflammation

In healthy prostatic tissue, a small number of lymphocytes can be observed in the glandular epithelium and around the ducts. T lymphocytes account for more than 90% of these infiltrating cells and are predominantly of the Cluster of Differentiation 8+ (CD8+) subtype, accompanied by a small number of macrophages. In the fibromuscular stroma, lymphoid aggregates are present, consisting of a central core containing 60% B lymphocytes and a surrounding parafollicular area composed of 40% T lymphocytes, mainly of the CD4+ subtype [7]. Conversely, in prostate tissues with chronic inflammation, T lymphocytes are markedly increased and are predominantly of the CD4+ subtype. In addition, approximately 30% of other inflammatory cells, including B lymphocytes, macrophages, and mast cells, infiltrate the glands, periglandular areas, and stromal compartments. The composition and distribution of these immune cells differ substantially from those observed in healthy prostate tissue [4]. Aberrant infiltration of inflammatory cells indicates disruption of local immune homeostasis and may contribute to the development and progression of BPH.

Macrophages play an important role in the progression of prostatic hyperplasia. They not only promote proliferation of prostatic epithelial cells by secreting cytokines that activate the extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) signaling pathways [8], but also regulate the expression of the androgen receptor (AR) and CD40/CD40L through activation of the mitogen-activated protein kinase (MAPK) pathway, thereby promoting inflammation and cellular proliferation while inhibiting apoptosis in BPH tissues [9]. Macrophages are broadly classified into M1 macrophages (classically activated macrophages) and M2 macrophages (alternatively activated macrophages). M1 macrophages mainly secrete pro-inflammatory mediators during the early phase of inflammation, whereas M2 macrophages contribute to the suppression of inflammation and tissue repair through phagocytosis, as well as pro-angiogenic and pro-fibrotic phenotypes. M2 macrophages are the predominant inflammatory cells infiltrating BPH tissues and driving prostatic-cell proliferation, largely through secretion of cytokines and growth factors involved in disease progression [10]. Among these, the M2a subtype appears to be particularly important and may promote BPH progression by increasing expression of insulin-like growth factor 1 (IGF-1) [11]. Lanman *et al.* [12] reported that lipid-rich macrophage subpopulations accumulate in enlarged prostates and are positively associated with LUTS severity. Collectively, these findings support a multifaceted role of macrophages in BPH, although the precise mechanisms remain to be fully clarified.

Overall, immune-cell infiltration in BPH should not be regarded merely as a histological observation, but rather as an active component of a self-sustaining inflammatory microenvironment.

2.2 Cytokine network in the BPH microenvironment

The inflammatory microenvironment in BPH is shaped by a complex network of cytokines and chemokines, rather than by a single mediator. These inflammatory signals act in concert to promote immune-cell recruitment, aberrant remodeling of prostatic tissue, and disease progression. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that supports the growth of both epithelial and stromal cells. As a key mediator of paracrine and autocrine signaling, IL-6 promotes cellular proliferation and survival, thereby contributing to prostatic hyperplasia [13]. Elevated IL-6 levels are associated with increased prostate volume and more severe LUTS [14], suggesting that IL-6 may link inflammation to hyperplastic growth in BPH. Interleukin-8 (IL-8) is considered one of the most important cytokines involved in the initiation and progression of BPH and can directly stimulate proliferation of prostatic epithelial and stromal cells [15]. Compared with normal prostate tissue, the levels of IL-8 and its receptors are increased by 5- to 25-fold in BPH tissues, and gene-editing studies have further confirmed that the IL-8 axis directly promotes prostatic epithelial-cell growth [16]. In addition, IL-8 has been proposed as one of the most reliable indicators of prostatic inflammation, including chronic prostatitis and chronic pelvic pain syndrome/BPH, and is closely associated with IPSS and prostate-specific antigen (PSA) levels in patients with BPH [17]. Tumor necrosis factor alpha (TNF-α) is a key mediator of both systemic and local inflammation and promotes immune-cell activation and the production of inflammatory mediators. Elevated TNF-α levels are associated with increased tissue remodeling, fibrosis, and smooth muscle-cell proliferation in the prostate. TNF-α protein expression is significantly higher in patients with larger prostates than in those with smaller prostates [18], and clinical studies have shown a negative association between TNF-α inhibitor use and prostate growth rate [19]. In addition to IL-6, IL-8, and TNF-α, the IL-1 family, transforming growth factor beta (TGF-β), and various chemokines also contribute to BPH. Interleukin-1 beta (IL-1β) modulates immune responses and promotes fibrosis, whereas TGF-β supports stromal hyperplasia. Together, these mediators maintain a chronic inflammatory milieu in the prostate and drive tissue remodeling and disease progression [15]. Through extensive cross-talk, cytokines and chemokines sustain immune-cell recruitment, oxidative stress, and extracellular matrix remodeling. Such interactions amplify the inflammatory response and contribute to persistent tissue injury in BPH. In summary, cytokine dysregulation in BPH reflects a coordinated inflammatory network that drives tissue remodeling and disease heterogeneity, thereby providing new opportunities for immune-targeted therapeutic intervention.

3. Immune regulatory mechanisms and molecular signaling pathways

3.1 NF-κB signaling pathway

The nuclear factor kappa B (NF-κB) signaling pathway is a central regulatory axis in BPH-associated inflammation. Inflammatory cytokines such as TNF-α and IL-1β, as well as oxidative stress, metabolic disturbances, and microbe-related stimuli, can all activate NF-κB. Activated NF-κB subsequently induces downstream inflammatory mediators, including cyclooxygenase-2 (COX-2), while enhancing anti-apoptotic and pro-proliferative signaling, thereby promoting

persistent inflammation, increased cell survival, and abnormal proliferation within prostatic tissue [20]. Interactions between infiltrating immune cells and local prostatic epithelial and stromal cells may further amplify this process, leading to sustained chronic inflammation, stromal hyperplasia, and tissue remodeling. Thus, NF-κB mediates not only the inflammatory response itself, but also the molecular processes through which inflammation is translated into a hyperplastic phenotype. Clinical studies also suggest that NF-κB activation is associated with the degree of tissue hyperplasia in BPH. Immunohistochemical analyses of prostate tissues from 101 patients with BPH showed that NF-κB is expressed in both glandular and stromal compartments and that patients showing NF-κB activation have larger prostate volumes [21]. In addition, testosterone propionate may exacerbate prostatic inflammation and cellular proliferation through activation of the NF-κB pathway [22]. Together, these findings suggest that aberrant NF-κB activation contributes to persistent inflammation and prostatic remodeling in BPH. Based on these mechanisms, NF-κB is considered a potential anti-inflammatory therapeutic target. Experimental studies have shown that several natural compounds, such as extracts of Celtis choseniana Nakai and resveratrol, can attenuate inflammatory responses and inhibit prostatic-cell proliferation by suppressing NF-κB-related signaling [23, 24]. However, because NF-κB is broadly involved in physiological immune regulation, the specificity, long-term safety, and clinical translational value of NF-κB-targeted therapy in BPH require further investigation. NF-κB may represent a key converging node linking multiple inflammatory stimuli to persistent prostatic remodeling.

3.2 NLRP3 inflammasome

As a key amplifier of inflammatory signaling, the inflammasome has attracted considerable attention, particularly the NLR family pyrin domain containing 3 (NLRP3) inflammasome, an intracellular multiprotein cytoplasmic complex that belongs to the innate immune system. Studies have shown that complement component C5a activates the NLRP3 inflammasome, thereby promoting caspase-1-dependent production of IL-1β and IL-18 and contributing to stromal proliferation in BPH [25]. NLRP3 may originate from prostatic stromal cells, especially myofibroblasts. Wang *et al.* [26] also demonstrated, by immunohistochemical analysis, that NLRP3 inflammasome expression is significantly higher in BPH tissues than in healthy prostate tissue and further confirmed that modulation of the NLRP3 inflammasome can attenuate inflammation and oxidative-stress injury in BPH. Inhibition of the NLRP3 inflammasome by resveratrol has been shown to reduce prostate volume. In addition, resveratrol and the antioxidant mitoquinone may slow BPH progression by suppressing NLRP3-related signaling pathways [25, 27]. Therefore, NLRP3 may represent a critical node linking inflammatory amplification to persistent prostatic remodeling, although the current evidence still requires confirmation in larger studies with stronger clinical relevance.

3.3 Th17/IL-17 axis

Adaptive immune dysregulation also contributes to the maintenance of the inflammatory microenvironment in BPH-associated chronic inflammation. In recent years, the imbalance between T helper 17 (Th17) cells and regulatory T (Treg) cells has attracted considerable attention. Th17 cells are characterized by secretion of IL-17, which promotes neutrophil recruitment and amplifies local inflammatory responses, whereas Treg cells primarily mediate immunosuppression and maintain immune tolerance and inflammatory balance. Disruption of this dynamic equilibrium may drive the transition of local prostatic inflammation from a transient response to a persistent chronic inflammatory state. Previous studies have shown that, compared with normal prostate tissue, BPH tissues exhibit increased Th17-cell infiltration and overexpression of IL-17A mRNA [28, 29]. IL-17 not only participates in inflammatory-cell recruitment, but also induces the release of additional pro-inflammatory cytokines and chemokines, thereby enhancing cytokine cascades and sustaining chronic tissue inflammation. In the context of BPH, IL-17-related responses may not only reflect local inflammatory activation, but also contribute to hyperplastic progression by strengthening epithelial-stromal interactions and amplifying pro-inflammatory signaling. Radej *et al.* [30] isolated Propionibacterium acnes from BPH and PCa tissues and proposed that this bacterium may stimulate malignant-cell proliferation by inducing IL-17 secretion from Th17 cells, while also promoting the formation of an inflammatory microenvironment through disruption of Th17/Treg balance, thereby contributing to both BPH and PCa development [31]. Th17/Treg imbalance may also link BPH to other inflammatory prostatic disorders. Current evidence suggests that this immune dysregulation is observed not only in BPH, but also in chronic prostatitis- and chronic pelvic pain syndrome-associated inflammatory settings, indicating the existence of partially overlapping inflammatory phenotypes among different prostatic diseases [32]. Peripheral-blood studies also support this trend, showing that the proportion of Th17 cells and the Th17/Treg ratio are elevated in patients with BPH compared with healthy controls [33]. This finding suggests that the imbalance may not be confined to local tissue, but may also reflect a systemic inflammatory bias. Nevertheless, current evidence mainly indicates an association between Th17/Treg abnormalities and BPH-related inflammation. Their precise role in different clinical phenotypes of BPH, their utility as stable prognostic biomarkers, and their similarities to or differences from the inflammatory microenvironment of prostate cancer all require further study.

Overall, current evidence suggests that the Th17/IL-17 axis and Th17/Treg imbalance may participate in maintaining chronic inflammation in BPH and promote local tissue remodeling through the inflammation-amplifying effects of IL-17. However, the specific contribution of this immune axis to different BPH phenotypes has not yet been fully defined.

3.4 TGF-β

Transforming growth factor beta (TGF-β) is a multifunctional polypeptide cytokine that plays important roles in BPH progression by promoting epithelial-mesenchymal transition (EMT), prostatic fibrosis, and inflammation, and is considered one of the most active regulators driving disease progression and symptom development. Binding of TGF-β to its receptors activates Smad signaling, which induces fibroblast differentiation into myofibroblasts, promotes extracellular-matrix formation and deposition, and ultimately leads to fibrosis [34]. At the same time, TGF-β may further aggravate TGF-β-induced fibrosis by promoting the production of inflammatory mediators such as IL-6 and TNF-α through downstream NF-κB signaling and by inducing oxidative stress. Wang *et al.* [35] found that TGF-β1 can also impair the epithelial barrier of the prostate by downregulating the tight-junction protein claudin-1 via the Mitogen activated protein kinase kinase (MEK)/Extracellular signal-regulated kinase (ERK) pathway. Blockade of TGF-β signaling has been considered an effective therapeutic strategy in multiple diseases and has also attracted attention in BPH research. For example, neferine can alleviate BPH progression by inhibiting TGF-β-mediated EMT and oxidative stress [36], whereas hesperidin improves BPH by modulating the TGF-β/Smad signaling pathway, thereby attenuating cellular proliferation, inflammation, and EMT [37]. These findings suggest a promising therapeutic avenue for BPH.

Collectively, these pathways should not be interpreted as isolated molecular events. Instead, they form an interconnected signaling network through which inflammatory stimuli are translated into persistent proliferation, remodeling, and clinical progression.

4. Inflammation and systemic pathological status

4.1 Metabolic syndrome and inflammation

Metabolic syndrome (MetS) is not a single disease, but rather a cluster of coexisting and interrelated metabolic abnormalities, including central obesity, hypertension, elevated fasting glucose, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol (HDL-C). Growing evidence suggests that MetS is not only an important background factor for cardiovascular disease and diabetes, but may also provide a systemic inflammatory basis for the development and progression of BPH/LUTS. Epidemiological studies have shown that older Chinese men with MetS have a 1.60-fold higher risk of developing BPH/LUTS than those without MetS, and this association is particularly evident for low HDL, abdominal obesity, elevated triglycerides, and hyperglycemia [38]. Meanwhile, multiple studies have demonstrated associations between MetS and increased prostate volume as well as progression of LUTS, with inflammation serving as a central mediating mechanism. Prostatic inflammation is negatively correlated with heme oxygenase-1 and HDL levels in prostatic tissue and positively correlated with triglyceride levels [39]. Patients with BPH complicated by MetS exhibit significantly higher immunoexpression of IL-6 and IL-18 in prostatic tissue than patients with BPH alone [13]. Gacci *et al.* [40] reported that patients with both MetS and BPH have significantly higher grades of prostatic inflammation than those without MetS, and that elevated serum triglycerides and lower HDL-C levels are associated with an increased risk of prostate volume $\geq$60 mL. Diverse pathogenic pathways contributing to MetS ultimately converge on a state of chronic low-grade inflammation, leading to elevated inflammatory markers such as C-reactive protein (CRP) and pro-inflammatory cytokines including IL-8 and IL-6. This chronic inflammation induces tissue injury and repetitive wound-healing responses, ultimately promoting the development of BPH [41, 42]. Insulin and insulin-like growth factor 1 (IGF-1) can inactivate the alpha and beta subunits of glycogen synthase kinase-3 through phosphorylation, thereby increasing the expression of IL-17-induced inflammatory cytokines and chemokines and ultimately amplifying intraprostatic inflammation [43]. In obesity-induced inflammation, aberrant secretion of inflammatory cytokines and chemokines can also accelerate inflammatory progression within the prostate. An animal study showed that excessive fat intake activates signal transducer and activator of transcription 3 (STAT3) and NF-κB in the prostate, increases IL-6 expression, and aggravates intraprostatic inflammation [44], whereas caloric restriction reduces immune-inflammatory infiltration and tissue remodeling in rat prostate tissue [45]. Overall, the association between MetS and BPH is biologically plausible and is increasingly supported by both clinical and experimental evidence. However, because the components of MetS frequently cluster with aging and other comorbidities, the causal relationship between MetS and BPH remains difficult to fully disentangle. MetS may promote BPH/LUTS progression through systemic low-grade inflammation, dysregulated metabolic signaling, and local tissue remodeling, but the magnitude of this effect and its contribution to different BPH phenotypes still require further clarification.

4.2 Microbial community and inflammation

4.2.1 Gut microbiota

In recent years, increasing evidence has suggested that the gut microbiota may contribute to the progression of prostatic diseases through multiple mechanisms, supporting the existence of a “gut-prostate axis” [46]. Li *et al.* [47], using 16S rDNA sequencing and liquid chromatography-tandem mass spectrometry, found that BPH is associated with alterations in both gut microbial diversity and intestinal metabolomics. Dysbiosis of the gut microbiota can lead to abnormal immune responses, which are often accompanied by aberrant production of inflammatory cytokines [48]. Gut microbial dysbiosis may increase the production of inflammatory mediators such as IL-17, IL-23, and TNF-α; these cytokines can subsequently reach distant organs, including the prostate, through circulation and thereby alter the local prostatic microenvironment, contributing to prostatic disease [49]. Certain gut microbes produce substances that help maintain intestinal-barrier integrity.

When gut microbial dysbiosis occurs, the intestinal barrier may be disrupted, allowing translocation of microorganisms and their metabolites from the gut and potentially triggering systemic inflammatory responses [50]. Lipopolysaccharide (LPS) may play an important role in this process by mediating prostatic inflammation through microbiota-associated molecular patterns. Binding of LPS to Toll-like receptors upregulates NF-κB and pro-IL-1β expression and promotes the maturation and secretion of IL-1β and IL-18. The gut microbiota may also indirectly affect the prostate through short-chain fatty acids (SCFAs), thereby influencing the prostatic inflammatory microenvironment [13]. With the expanding study of microbiota in prostatic diseases, the role of probiotics has also received increasing attention. Liu *et al.* [51] reported that increasing colonization of Akkermansia muciniphila in mice with prostatitis enhanced SCFA levels, lowered serum LPS levels, and alleviated prostatitis progression. Another study showed that both heat-killed and live Enterococcus faecalis can modulate androgen-signaling factors, growth factors, and apoptosis-related factors in prostatic tissue, thereby suppressing prostatic hyperplasia [52]. These findings provide new perspectives for BPH prevention and treatment, suggesting that interventions targeting the gut microbiota, such as probiotics and dietary supplementation, may hold promise in prostatic diseases.

4.2.2 Urinary microbiota

A large body of research has reported associations between the urinary microbiota and urgency urinary incontinence (UUI), interstitial cystitis (IC), and bladder pain syndrome (BPS). The urinary microbiota may participate in BPH pathogenesis through acute or chronic inflammation, in which inflammasomes and microbiota-derived metabolites play important roles [53, 54]. Lee *et al.* [55] found that certain bacteria, such as Haemophilus and Staphylococcus, are associated with LUTS severity and proposed that dysbiosis of the urinary microbiota plays an important role in BPH progression. Li *et al.* [56], using metagenomic next-generation sequencing, identified differences in microbiome composition between normal prostatic tissues and BPH tissues, with Pseudomonas being markedly enriched in BPH tissues. Their *in vitro* experiments further showed that Pseudomonas-derived LPS can activate NF-κB signaling, leading to inflammation, proliferation, and EMT, while simultaneously inhibiting apoptosis of prostatic cells. In the study by Jain *et al.* [57], viable bacteria were detected in the prostatic tissues of 55.5% of patients with BPH. Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes were the most common phyla identified in BPH tissues, and these bacteria were considered potential contributors to BPH-related inflammation and tissue injury. Their *in vitro* experiments also showed that Escherichia coli can induce NF-κB signaling and DNA damage in prostatic epithelial cells. Although preliminary findings suggest that the urinary microbiota may exert multiple effects, studies in this area remain far fewer than those on the gut microbiota, and mechanistic evidence is still limited. More experimental work is therefore needed to clarify the role of the urinary microbiota in prostatic disease.

5. Clinical translation: inflammation as a therapeutic and diagnostic opportunity

Inflammation is involved throughout the development and progression of BPH. In this context, inflammation-related indices may provide additional support for clinical assessment and therapeutic decision-making. Multiple studies have shown that systemic inflammatory indices are closely associated with BPH severity and related LUTS. Elevated systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and neutrophil-to-lymphocyte ratio (NLR) are all associated with more severe BPH, with SII showing superior discriminatory performance [58, 59]. Therefore, incorporating indices such as SII into clinical evaluation may aid in risk stratification, treatment selection, and disease monitoring in patients with LUTS/BPH [60]. However, these indices currently mainly reflect systemic inflammatory status, and their specificity and clinical stability still require further validation; thus, they cannot yet be used alone to guide treatment decisions. More realistically, they may in the future help identify patients with a more pronounced inflammation-driven phenotype, thereby supporting selection and response monitoring of anti-inflammatory combination therapy.

Anti-inflammatory therapy may reduce inflammation-related abnormal tissue hyperplasia by intervening in different inflammatory pathways and therefore represents a potential treatment strategy for BPH. Previous studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) can improve LUTS in patients with BPH [61, 62]. Compared with 5-alpha-reductase inhibitor (5-ARI) monotherapy, combination therapy with NSAIDs and 5-ARIs may provide faster symptom relief and improve maximum urinary flow rate [63]. On the other hand, retrospective cohort studies and Mendelian-randomization analyses have suggested that NSAID use may increase the risk of BPH [64, 65], and other cohort studies have not supported a protective effect [66]. Therefore, NSAIDs are not recommended as routine long-term therapy for patients with BPH, although short-term use may be considered when overt inflammatory symptoms are present. Inamura *et al.* [67] found that the duration of 5-ARI treatment is positively associated with the degree of prostatic inflammation, possibly because of attenuation of the anti-inflammatory effects of dihydrotestosterone (DHT) mediated through AR and because 5-ARIs may cause local ischemia in the prostate. This finding suggests that 5-ARI monotherapy may be insufficient to adequately improve the inflammatory microenvironment and that combination therapy with other anti-inflammatory approaches may be more beneficial. Existing clinical studies have provided preliminary support for combination treatment. A single-center randomized controlled study showed that anti-inflammatory therapy combined with finasteride and tamsulosin further improved quality of life, erectile function, and IPSS compared with the either drugs alone [68]. Beyond conventional anti-inflammatory drugs, therapies targeting specific inflammatory pathways have also shown promise. Retrospective studies have found that previous use of TNF-α inhibitors is associated with smaller prostate volume and slower prostate growth [19].

Vickman *et al.* [69] further demonstrated that TNF antagonists reduce the risk of BPH in patients with autoimmune diseases and, *in vitro*, that TNF promotes proliferation of BPH-derived fibroblasts, whereas TNF blockade reduces epithelial hyperplasia, NF-κB activation, and macrophage-mediated inflammation [69]. In addition, the potential value of phytochemicals in the anti-inflammatory treatment of BPH has attracted increasing attention. Randomized controlled studies have shown that phytochemicals combined with fluoroquinolones are more effective than monotherapy in improving inflammatory symptoms related to prostatitis [70]. At the same time, some natural compounds and traditional Chinese medicine preparations can attenuate inflammation and delay BPH progression by modulating NF-κB signaling and NLRP3 inflammasome activation [23, 24, 71]. Overall, inflammation plays an important role in BPH pathogenesis, and early anti-inflammatory intervention may help alleviate symptoms and delay disease progression. The combination of standard therapy with anti-inflammatory approaches appears promising; however, the current evidence remains limited and is derived mainly from retrospective studies, small-sample investigations, or mechanistic research. Clinical endpoints and long-term safety still require further validation. Future high-quality studies are needed to determine the populations most likely to benefit from different anti-inflammatory strategies and to define their efficacy and safety in BPH.

6. Summary and outlook

Chronic inflammation is considered an important driver of BPH development and clinical progression. Immune cells within prostatic tissue regulate local immune responses through multiple signaling pathways, inflammatory mediators, and chemokines, leading to inflammatory infiltration, tissue damage, and aberrant repair, thereby promoting prostatic hyperplasia. More importantly, chronic inflammation does not occur in isolation; rather, it represents a key mechanism linking immune dysregulation, metabolic disturbance, microbiota imbalance, fibrosis, and tissue remodeling in BPH. Although increasing evidence supports the role of chronic inflammation in BPH, its clinical translation remains limited. Most existing data are derived from animal models, *in vitro* experiments, and observational studies, whereas high-quality randomized controlled trials specifically targeting inflammatory pathways in BPH are still lacking. In addition, factors such as aging, metabolic syndrome, diabetes, obesity, and concomitant medication use may independently influence inflammatory status and symptom severity, complicating the interpretation of the current findings and their extrapolation to clinical practice. From a therapeutic perspective, targeting inflammation provides a new direction for BPH intervention, but at present it is better considered a complement to standard treatment rather than a substitute. Compared with alpha-adrenergic receptor blockers and 5-alpha-reductase inhibitors, which mainly improve dynamic obstruction or suppress androgen-dependent hyperplasia, the potential value of anti-inflammatory therapy lies in modulation of the inflammatory microenvironment, attenuation of tissue remodeling, and possible delay of disease progression. However, direct clinical evidence supporting anti-inflammatory therapy combined with alpha-blockers or 5-ARIs remains limited and comes mainly from small randomized studies or observational analyses, and the efficacy and safety data are still insufficient to justify widespread clinical application. Therefore, anti-inflammatory strategies should currently be viewed as promising adjunctive approaches, particularly for patients with a pronounced inflammatory phenotype, metabolic abnormalities, or a suboptimal response to standard therapy. Future studies should aim to identify reliable inflammation-related biomarkers, establish clinically meaningful patient-stratification systems, and systematically evaluate the long-term efficacy and safety of anti-inflammatory combination therapy in multicenter, prospective, randomized controlled trials, thereby clarifying its practical value in precision treatment of BPH.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YFL—Writing the manuscript. DJS—Literature review. HCW—Literature review. RYL—Provided help and advice on the revision of the paper. XZY—Revising the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

We would like to express our gratitude to all of the people who helped during the writing of this manuscript, and to the peer reviewers for their constructive opinion and suggestions.

FUNDING

(1) Shanxi Provincial Health Commission's "Four Batches" Science and Technology Driven Medical Innovation Plan Project (2022XM22); (2) Wu Jieping Medical Foundation Clinical Research Special Fund Project (320.6750.2022-02-40); (3) 2024 Shandong Province Geriatric Society Science and Technology Key Plan Project (LKJGG2024W048).

CONFLICT OF INTEREST

The authors declare no conflict of interest. Xuezhen Yang is serving as one of the Editorial Board members of this journal. We declare that Xuezhen Yang had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to BB.

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How to cite this article: Yifan Lv, Dengjin Shi, Haicheng Wang, Rongyao Liu, Xuezhen Yang. Inflammatory and immunomodulatory regulatory mechanisms in benign prostatic hyperplasia. Journal of Men's Health. 2026; 22(8): 17-24. doi: 10.22514/jomh.2026.066.