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The Role of Inflammation in Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH) and Its Potential Impact on Medical Therapy

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Abstract A chronic prostatic inflammation seems to play a crucial role in benign prostatic hyperplasia (BPH) pathogenesis and progression. Therefore, inflammation could represent a new potential target for medical therapy of lower urinary tract symptoms (LUTS) due to BPH (LUTS/BPH). This review article analyzes the evidence supporting the role of inflammation in the onset and progression of BPH, and it assesses the potential impact of previous mechanisms on medical therapy of LUTS/BPH. Literature data support the role of inflammation as a relevant factor in the pathogenesis of BPH. Indeed, several data favour the role of infiltrating lymphocytes in the development and progression of prostate adenoma as an effect of a self-maintaining remodeling process. Although available drugs commonly used in the treatment of LUTS/BPH do not exhibit an anti-inflammatory activity, it seems to be obvious considering the inflammation as a new target in the treatment of LUTS/BPH. Drugs currently investigated for the treatment of prostatic inflammation include the hexanic lipidosterolic extract of *Serenoa* repens, nonsteroidal anti-inflammatory drugs, and vitamin D receptor agonists.

Keywords Inflammation · Lower urinary tract symptoms · Benign prostatic hyperplasia · Medical therapy

This article is part of the Topical Collection on *Benign Prostatic Hyperplasia*

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Introduction

The role of androgens and growth factors in the onset and progression of benign prostate hyperplasia (BPH) has been well reported over the last few decades. In detail, androgens promote prostatic cell proliferation and inhibit programmed cell death. Similarly, some growth factors, such as keratinocyte growth factor (KGF), epidermal growth factor (EGF), and insulin-like growth factor, stimulate prostatic cell proliferation and others, such as transforming growth factor-1 (TGF-1), promote apoptosis. Recent in vitro, in vivo, and clinical studies suggested that infiltrating inflammatory cells might act as a link between hormonal changes and the remodeling process promoted by growth factors. Therefore, a chronic prostatic inflammation seems to play a crucial role in BPH pathogenesis and progression [1]. Specifically, hormonal changes may promote an increased presence of inflammatory infiltrate in the prostate responsible for a tissue damage both at level of epithelial and stromal cells initiating a chronic process of wound healing which, in turn, might determine prostatic enlargement [2]. Moreover, the prevalence of chronic prostatic inflammation in patients with lower urinary tract symptoms (LUTS)/BPH has been estimated in the context

of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. According to the protocol of this randomized, double-blind, placebo-controlled trial, 8224 patients underwent a prostate biopsy at study entry before being randomized to dutasteride or placebo. In this cohort of patients, chronic prostatic inflammation was detected histologically in 77.6 % of cases, with the majority (89 %) of these biopsy specimens showing mild chronic inflammation [3].

According to the previous pathogenic models and clinical data, chronic prostatic inflammation could represent a new potential target for medical therapy of LUTS due to BPH (LUTS/BPH). The objective of this review article is twofold: (1) to analyze the evidence supporting the role of inflammation in the onset and progression of BPH and (2) to assess the potential impact of previous mechanisms on medical therapy of LUTS/BPH.

Role of Inflammation in BPH

Normal prostate is an immunocompetent organ populated by a limited number of inflammatory cells consisting of scattered stromal and intraepithelial T and B lymphocytes, macrophages, and mast cells. In detail, T lymphocytes (70 % CD8 cells) are mainly located around the periglandular area, while lymphoid aggregates are located in the fibromuscular stroma. These aggregates, consisting mainly of B lymphocyte follicles surrounded by parafollicular T cells with CD4 cells, are twice more frequent than CD8 cells [4•]. In the adult prostate, a different inflammatory infiltrate pattern has been described according to the inflammation characteristics. In detail, inflammatory infiltrates are mostly represented by CD3+ T lymphocytes, CD19 or CD20 B lymphocytes, and macrophages. The phenotype of T cells also shows a reverse CD8-to-CD4 ratio. Therefore, most T cells in the inflammatory areas express CD4 [5, 6].

Although the stimulus for an inflammatory response in the prostates of older males is not fully understood, it is likely to be multifactorial. Potential causes include hormonal changes, infections (bacterial or viral), dietary or environmental factors, autoimmune response, urinary reflux inside prostate collecting ducts, and systemic inflammation associated with the metabolic syndrome [7•]. Regardless of the primum movens, T lymphocytes, macrophages, and B lymphocytes that are present in the adult prostate can generate damage of both epithelial and stromal cells, stimulating cytokine release and increasing the concentration of growth factors that promote an abnormal remodeling process characterized by fibromuscular growth. In detail, infiltrating lymphocytes promote the release of IL-2, IFN-γ, FGF-2, and TGF-β that are directly responsible for fibromuscular growth and/or stimulate IL-6, IL-8, and IL-17 production. These interleukins can induce a prostate fibromuscular growth through an autocrine and paracrine loop or can perpetuate a chronic immune response mechanism stimulating again lymphocytes and/or macrophages. The final result is a localized "vicious cycle" that leads to a progressive increase in prostate volume [1, 7•, 8]. A significant effect of this remodeling process inducing an abnormal prostatic enlargement is local hypoxia, which is responsible for the release of reactive oxygen species (ROS) that can promote neovascularization and further release of vascular endothelial growth factors (VEGFs), i.e., VEGF, IL-8, FGF-7, transforming growth factor [TGF]-b, and FGF-2 [9••]. These growth factors may interact not only with inflammatory cells but also with the stromal and epithelial cells of the prostate, increasing prostatic enlargement.

How to Evaluate Chronic Prostatic Inflammation

The histologic diagnosis of chronic prostatic inflammation can only be obtained in patients who have undergone a prostate biopsy for suspected prostate cancer. However, the high prevalence of chronic prostatic inflammation in patients with LUTS/BPH makes it imperative for clinicians to identify this condition also in patients who are not candidates for prostate biopsy. Currently, biomarkers represent a potential noninvasive alternative to prostate biopsy in the detection of chronic prostatic inflammation. Specifically, IL-8 in seminal plasma, monocyte chemotactic protein-1 (MCP-1) in prostatic secretion, and chemokine (C-C motif) receptor 7 (CCR7), cytotoxic T lymphocyte-associated antigen (CTLA4), inducible T cell costimulator (ICOS), and CD40 ligand (CD40LG) in urine have been evaluated as promising biomarkers predictive of chronic prostatic inflammation. However, more robust evidence from prospective clinical studies is required before these biomarkers can be introduced into routine clinical practice as an aid in diagnosis and surveillance of chronic prostatic inflammation [9••].

In the absence of biopsy data, the presence of a significant amount of infiltrating lymphocytes in the prostatic tissue could be suspected in patients with prostatic calcifications and/or severe storage symptoms and/or metabolic syndrome.

Prostatic calcifications are present in around 47 % of symptomatic patients younger than 50 years and in 86 % of symptomatic patients older than 50 years [7•]. This age-related difference in prevalence may be explained by different etiologic mechanisms. In younger men, calcifications can be formed by prostatic fluid alterations promoted by infections or inflammatory prostatic disease (e.g., prostatitis). Conversely, in older men, prostatic fluid alterations generally seem to be consequent to an age-related alteration. Prostatic calcifications lead to an obstruction of intraprostatic ducts and an accumulation of inflammatory substances in prostatic secretions that stimulate an inflammatory reaction in prostatic tissue through

a damage of epithelial and stromal cells and a healing process characterized by stromal proliferation and excessive extracellular matrix production [8].

Concerning symptom severity, a post hoc analysis of the REDUCE trial showed a statistically significant correlation between chronic prostatic inflammation in the biopsy specimens and total IPSS score and voiding and storage (statistically more relevant) IPSS subscales [3]. The relationship between storage symptoms and prostatic inflammation status was further confirmed by Robert et al. in an observational study evaluating specimens from transurethral resection of the prostate [10].

In addition to the above symptoms and signs, the presence of prostatic infiltrating lymphocytes can be suspected also in patients with metabolic syndrome. Indeed, this syndrome promotes LUTS/BPH through four key steps: insulin resistance, hormone changes, pelvic atherosclerosis, and inflammation. Specifically, patients with metabolic syndrome have high levels of inflammatory cytokines that are responsible for LUTS/BPH [11].

Therefore, in patients who are not candidates for prostate biopsy, the presence of a relevant inflammatory status responsible for a continuous remodeling process in the prostate can be suspected in patients with prostatic calcifications and/or severe storage symptoms and/or metabolic syndrome.

Impact of Inflammation on Medical Therapy for LUTS/BPH

Due to its role in the pathogenesis and progression of BPH, inflammation should be considered as a new rational target for medical therapy for LUTS/BPH.

Alpha1-blockers and 5-alpha reductase inhibitors (5-ARIs) as monotherapy or in combination represent the most frequently used drugs in the treatment of LUTS/BPH. Both are recommended in the treatment of patients with moderate-to-severe LUTS. Moreover, considering the rapid onset of action of alpha1-blockers and the slow onset of action of 5-alpha reductase inhibitors, their combination offers an excellent opportunity to improve symptoms and to prevent disease progression [12]. However, these treatments show some limitations. The adverse event profile of 5-ARIs could be a limitation for long-term treatment for a consistent number of patients. Overall, up to 10 % of patients treated with 5-ARIs report sexually related events. In details, erectile dysfunction, decreased libido, and decreased volume of ejaculate occur nearly twice than that in placebo, particularly during the first year of treatment [13]. Moreover, 5-ARIs may lose their efficacy during chronic inflammation. Indeed, the inflammation produces IL6 and IL8 that stimulate the receptors AR, increasing the growth factors release. The consequent vicious circle is maintained independently of the therapy with 5-ARIs. Furthermore, interleukins induce the transformation from fibroblasts into myofibroblasts through a process of transdifferentiation, which produces FGF and ROS. The ongoing repair leads to tissue remodeling. Figure 1 shows the potential mechanism related to inflammation able to activate and maintain a vicious circle promoting BPH progression in patients continuously treated with 5-ARIs (Fig. 1).

Although a1-blockers decrease the risk of overall clinical BPH progression (regarding all events), they do not reduce the risk of specific progression events including the rate of acute urinary retention, the need for invasive therapy, or serum PSA levels. Additionally, the efficacy of a1-blockers seems to decrease over time [14]. Moreover, inflammatory mediators such as thromboxane A2 (TXA2) mediate smooth muscle contraction by activation of calcium- and Rho kinase-dependent signaling pathways, that is, the same intracellular effectors are used by a1-adrenoceptors to induce prostate

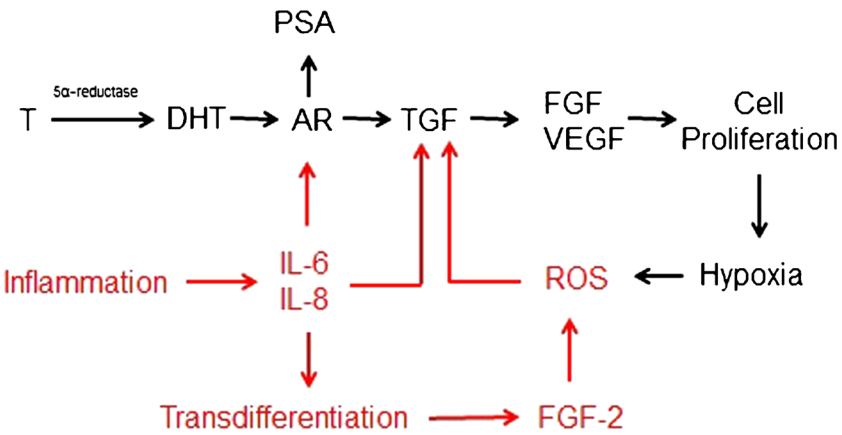

Fig. 1 Role of inflammation in adult prostate. Presence of an inflammatory status is able to stimulate IL-6 and IL-8 production. Interleukins are able to stimulate androgen receptors independently by DHT, as well as TGF synthesis. Therefore, infiltrating lymphocytes (inflammation condition) can maintain tissue proliferation also in the presence of 5α reductase inhibitors. Interestingly, proliferation and hypoxia can stimulate ROS production, further supporting a vicious circle

contraction [15, 16]. Thus, a1-adrenoceptors and the TXA2-R share common intracellular mediators to induce smooth muscle contraction in the prostate. This might explain why the effect of a1-blockers on BPO and LUTS is limited during inflammatory status. If TXA2 or other nonadrenergic mediators are released as paracrine mediators and induce contraction, blocking only a1-adrenoceptors should indeed be insufficient for complete prevention of contraction. Looking at the mode of action of both drugs, no anti-inflammatory activity is to be recognized.

In an interesting clinical study, Kwon et al. observed that in patients with high-grade prostatic inflammation, the use of a-blockers with 5-ARIs can be insufficient to reduce symptom severity. In detail, the authors prospectively enrolled 82 patients who were stratified in two groups according to findings at transrectal prostate biopsy, i.e., absent/low-grade versus high-grade chronic inflammation. All patients received combination therapy with alpha1-blocker and 5-ARI and were prospectively evaluated at baseline, 1, 3, 6, and 12 months after medical treatment. Patients with high-grade chronic inflammation reported significantly lower changes in IPSS and storage symptom scores over the 12-month follow-up period compared with patients with low-grade inflammation. Moreover, patients with low-grade inflammation demonstrated continuous improvement of storage symptoms until 12 months. Conversely, those in the high-grade group showed improvement until 3 months only. Maximal QoL improvements were observed at 6 months in the high-grade inflammation group and at 3 months in the low-grade inflammation group [17••].

Although this study is based on a small sample size and its results should be further confirmed, it seems to be rational to plan a new therapeutic option to block the effects of chronic prostatic inflammation in patients with LUTS/BPH.

Drugs with Anti-inflammatory Effect

In a recent review of literature, de la Taille analyzed the evidence for the use of various drug classes to reduce and prevent prostatic inflammation [18••]. Specifically, in this review, the author investigated the potential role of nonsteroidal anti-inflammatory drugs (NSAIDs) (especially cyclooxygenase-2 inhibitors), vitamin D receptor agonists, and extracts of *Serenoa repens*.

NSAIDs act at different sites in the arachidonic acid cascade, inhibiting the actions of phospholipase A2, cyclooxygenase, and prostacyclin synthetase enzymes. Various studies demonstrated the clinical efficacy of traditional NSAIDs and cyclooxygenase-2 (COX-2) inhibitors to relieve LUTS/BPH. A recent meta-analysis of three RCTs comparing NSAIDs versus placebo demonstrated that this class of drugs improved urinary symptom scores and flow measures over a treatment period of 4–24 weeks [19]. However, the most relevant drawback seems to be related to the clinical imperative to avoid long-term use of NSAIDs.

Prostate cells decrease their proliferation in response to vitamin D receptor (VDR) agonists, suggesting a role for VDR ligands in the treatment of LUTS/BPH. The calcitriol analog elocalcitol (BXL628) has been the most extensively studied VDR agonist to date [20]. However, despite evidence suggesting VDRs as potential therapeutic target for BPH, no VDR agonists are currently available for clinical use to treat prostatic inflammation.

Extracts of *S. repens* have been used for many years in the medical therapy of LUTS/BPH [21]. Many different and heterogeneous extracts are available. The hexanic lipidosterolic extract of *S. repens* (Permixon) is the drug more extensively studied in the context of basic research and clinical trials. Beyond the well-known anti-androgenic activity, the hexanic extract of *S. repens* is able to exert also an antiproliferative and an anti-inflammatory activity [18••]. Several experimental studies conducted using the hexanic extract of *S. repens* showed that this drug is able to block the arachidonic acid cascade by decreasing the production of prostaglandins and leukotrienes and to modify inflammatory status by decreasing B lymphocyte infiltrates and IL-1b and tumor necrosis factor (TNF)-a levels, increasing the expression of anti-inflammatory genes, and decreasing the expression of proinflammatory genes [18••]. Moreover, a recent study demonstrated that the hexanic extract of *S. repens* decreases the production of monocyte chemotactic protein-1 and the expression of vascular cell adhesion molecule-1 in human prostate and vascular cells in an inflammatory environment [22]. However, a single clinical study published in 2003 correlated the significant reduction in B lymphocytes and IL-1b and TNF-a levels with a significant improvement in clinical symptoms in patients treated with hexanic extract of *S. repens* prior to surgery (TURP or adenomectomy) [23]. Additional information about these relevant clinical aspects could be obtained by an ongoing clinical trial (PERMIN study) (ClinicalTrials.gov identifier NCT01604811). This 6-month study randomizing patients with LUTS/BPH to treatment with hexanic extract of *S. repens* 160 mg twice daily or tamsulosin 0.4 mg daily is expected to provide data concerning the effect of hexanic extract of *S. repens* on serum and urine biomarkers of inflammation in correlation with its effects on LUTS measured with the International Prostate Symptom Score and maximum urinary flow rate [24].

Conclusions

Inflammation must be considered as a relevant factor in the pathogenesis of BPH. Indeed, several data support the role of infiltrating lymphocytes in the development and progression

of prostate adenoma as an effect of a self-maintaining remodeling process. Although available drugs commonly used in the treatment of LUTS/BPH have not an anti-inflammatory activity, it seems to be obvious considering the inflammation as a new target in the treatment of LUTS/BPH. Drugs currently investigated for the treatment of prostatic inflammation include hexanic lipidosterolic extract of *S. repens*, nonsteroidal anti-inflammatory drugs, and vitamin D receptor agonists. According to available clinical data and safety profile, the only practicable option in the context of a long-term therapy seems to be the use of hexanic lipidosterolic extract of *S. repens*. However, more clinical data are needed to support the use of hexanic lipidosterolic extract of *S. repens* in a context of an evidence-based medicine. Currently, the use of this drug should be considered empirical even if based on a sound premise.

Compliance with Ethics Guidelines

Conflict of Interest Prof. Vincenzo Ficarra reports a grant and personal fees from Pierre Fabre.

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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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