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REVIEW ARTICLE

Prostatic inflammation: a potential treatment target for male LUTS due to benign prostatic obstruction

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Abstract

Background The purpose of this narrative review is to evaluate the role of prostatic inflammation as a treatment target for lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) and provide an update on the available therapies.

Methods An extensive literature search was conducted for studies on established and investigational treatments with anti-inflammatory mechanism of action that has been assessed for the management of male LUTS due to BPO.

Results Data on phosphodiesterase 5 inhibitors, nonsteroidal anti-inflammatory drugs, vitamin D3 receptor analogs, phytotherapy, statins, and lifestyle changes have been reviewed and analyzed. Preclinical evidence has shown the anti-inflammatory effect of these treatments on prostate. However, there is a wide variation in the degree of mature of each therapy. In addition, there are significant differences between the studies in terms of design, number of patients, and duration of follow-up.

Conclusions Several drugs classes have been investigated for their impact on prostatic inflammation and improvement of male LUTS. The reviewed data support the rationale for use of agents that may alter and improve the inflammatory environment in the prostate in men with LUTS, but further high-quality long-term studies are required for the exact positioning of the new drugs in daily practice.

Background

Lower urinary tract symptoms (LUTS) in men have been historically associated with bladder outlet obstruction (BOO), as a result of benign prostatic obstruction (BPO), which is often caused by benign prostatic enlargement resulting from the histologic condition of benign prostatic hyperplasia (BPH) [1–3]. Recent studies have shown that male LUTS may have a multifactorial etiology and many urological and non-urological conditions also contribute to LUTS [2, 3]. However, prostate still plays the main role in the etiology of LUTS.

Several pathological processes, including androgen signaling, neural pathways, inflammation, and metabolic factors have been recently proposed for the pathogenesis of male LUTS. During the last years prostatic inflammation has gained the attention of researchers. Prostatic inflammation is a common histopathological finding after a prostate biopsy or a transurethral or even an open prostatectomy [4, 5]. In addition, Di Siverio et al. [6] described 43% cases with chronic inflammation, after prostate biopsies, while in the REDUCE trial, 77.4% of men with LUTS/BPH presented chronic inflammation on biopsy. However, the pathophysiological link of inflammation with LUTS and BPH is not clearly understood and immunological and inflammatory patterns have been proposed. The present narrative review will focus on the potential role of prostatic inflammation as an alternative treatment target for LUTS due to BPO and provide an update on the current knowledge on available therapies.

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Methods

We searched Pubmed and Scopus databases for all relevant publications analyzing the role of prostatic inflammation in the treatment of men with LUTS due to BPO up to August 31, 2017. The following Medical Subject Headings terms were used: prostatic inflammation and BPH or BPO, or LUTS in combination with the prespecified treatment modalities. Reference lists of relevant articles were hand searched to identify additional articles, and the "related articles" function in PubMed was used. There was no limit of year publication, but only papers in English were included. The identification of relevant abstracts and the selection of studies for this narrative review was performed independently by two of the authors (M.S. and S.G.) and any conflicts resolved by a third investigator (M.G.).

Results

Pathophysiology

Prostate is normally populated by inflammatory cells (leukocytes) in adult men the inflammatory infiltrates are mostly represented by T lymphocytes (70%), B lymphocytes (15%), and macrophages (15%). These cells secrete IL-2, IFN-γ, FGF-2, and TGF-β, which are directly responsible for fibromuscular growth, and stimulate of IL-6, IL-8, and IL-17 production. T-cells concentration is gradually increased, due to the action of the inflammatory cytokines and finally they are replaced by fibromuscular nodules [7, 8]. This could be considered as an immunological origin of prostatic enlargement.

The pro-inflammatory cytokines are released by the inflammatory cells and may, in parallel, induce cyclooxygenase-2 (COX-2) expression in BPH, which is associated with the increased cell proliferation [9]. There is evidence supporting that IL-17, an upregulator of COX-2, is overexpressed in patients with BPH, mainly produced by T cells [10]. Local hypoxia and low levels of macrophage inhibitory cytokine-1 in prostatic specimen with inflammation could be considered as precursors of BPH. Reactive oxygen species (ROS) seem to be released under hypoxia situations, leading to growth factors release and finally gland enlargement [9, 11].

Prostatic chronic inflammation has also been indicated as a candidate mechanism at the crossroad between metabolic syndrome (MetS), prostatic enlargement, and worsening of LUTS [12]. MetS has been considered as a cluster of risk factors for cardiovascular and metabolic complications, including visceral obesity, hypertension, hyperglycemia, low levels of high-density lipoprotein (HDL) cholesterol, and hypertriglyceridemia [13]. In a recent multicenter cohort of BPH patients treated with simple prostatectomy, MetS severity was associated with the severity of prostatic inflammation in BPH specimens [14]. In a retrospective study on 271 men with BPH, the number of MetS parameters was associated with prostate volume and the severity of inflammation was associated with the severity of urinary symptoms [15]. In particular, MetS can be considered a systemic inflammatory promoter: chronic inflammation-driven tissue remodeling and overgrowth is recognized to have a causative role in BPH/LUTS [16].

Lifestyle changes

The theory suggested that MetS may induce inflammation associated with BPH reinforces the position of behavioral modifications and lifestyle advice. The adjustment of lifestyle behavior, including physical activity and low-fat diet may represent the first treatment option for men with LUTS/BPH. Exercise—promoting weight loss, enhancing vascular flow, normalizing lipid, and lipoprotein serum concentrations and preventing heart disease—can alleviate the lower urinary tract (LUT). In particular, in a meta-analysis evaluating the impact of physical activity on LUTS, Parsons et al. [17] demonstrated that compared to the sedentary men, the OR for LUTS/BPH were 0.70 ($p = 0.14$), 0.74 ($p = 0.005$), and 0.74 ($p = 0.006$) for men with light, moderate, and heavy physical activity. In a prospective trial on 93 volunteers with prostate-specific antigen (PSA) 4–10 ng/ml and prostate cancer with Gleason Scores less than 7, patients were randomized to a comprehensive lifestyle change or to a usual care control group. Lifestyle change achieves a significant reduction of body weight and dyslipidemia, features associated with a remarkable reduction of PSA, suggesting the hypothesis of an anti-inflammatory activity [18].

Phosphodiesterase 5 inhibitors (PDE5Is)

The well-established association between LUTS and erectile dysfunction has stimulated research over the use of PDE5Is as a potential treatment for male LUTS. Several clinical trials on the efficacy of PDE5Is have been performed and data from systematic reviews showed that PDE5Is improve both urinary symptoms and erectile function, but with negligible improvement in flow rate (Table 1) [19, 20]. Therefore, the use of PDE5Is is recommended in men with moderate-to-severe LUTS with or without ED. Currently, only tadalafil 5 mg once daily has been officially licensed for the male LUTS treatment [2].

Interestingly, the exact mechanism of PDE5Is action is not yet clearly elucidated although their clinical utility for the management of male LUTS has been accepted and several mechanisms of action have been hypothesized.

Table 1 High level of evidence studies on the effect of treatments with anti-inflammatory properties on LUTS/BPO

Study	Treatment intervention/control	Type of study	Number of patients	Follow-up	δIPSS [WMD (95% CI)]	*p*-value	δQmax (ml/s) [WMD (95% CI)]	*p*-value
Cacci et al. [20]	PDE5I/placebo	Meta-analysis	1879/870	8–12w	−2.85 [−3.59, −2.10]	<0.0001	−0.01 [−0.58, 0.56]	Not significant
Kahokehr et al. [27]	Rofecovib plus finasteride/finasteride	Meta-analysis	23/23	4–6w	−2.89	<0.001	0.95	0.007
	Celecoxib/placebo		40/40					
	Tenoxicam plus doxazosin/doxazosin		29/28		[−3.84, −1.95]		[0.26, 1.63]	
Novara et al. [44]	HESr/placebo	Meta-analysis	122/133	4–12w	N/a	N/a	3.37 [1.71, 5.03]	<0.0001
	HESr/tamsulosin		442/446	12–52w	1.15 [−1.11, 3.40]	0.32	−0.16 [−0.60, 0.28]	0.48

BPO benign prostatic obstruction, *HESr* hexanic lipidosterolic extract of Serenoa repens, *IPSS* International Prostate Symptom Score, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PDE5I* phosphodiesterase type 5 inhibitor, *Qmax* maximum flow rate, *LUTS* lower urinary tract symptoms, *WMD*weighted mean differences

There is accumulating data that PDE5Is can improve LUT oxygenation, induce smooth muscle relaxation in the prostate and bladder, negatively regulate proliferation of LUT stroma, and decrease bladder afferent nerve activity mainly through nitric oxide–cyclic guanosine monophosphate (NO/cGMP) pathway, and RhoA/Rho-kinase signaling [19].

Recent evidence suggests that PDE5Is can also downregulate prostate inflammation. In a non-genomic animal model (high-fat diet rabbits) of MetS and associated prostate alterations, administration of tadalafil resulted in blunting of prostate inflammation and leukocyte infiltration, and reduction of hypo-oxygenation and fibrosis (muscle/fiber ratio) [21]. An in vitro study evaluated the effect of tadalafil and vardenafil on secretion of interleukin 8 (IL-8) induced by both inflammatory (tumor necrosis factor a, TNF-a) and metabolic stimuli in myofibroblast human BPH cells. Both tadalafil and vardenafil markedly suppressed IL-8 secretion induced by both types of stimuli [22]. In addition, PDE5 blockade resulted in downregulation of expression and secretion of interferon γ-induced protein 10, a key inflammatory factor which recruits inflammatory leukocytes and promotes BPH. These findings suggest an anti-inflammatory effect of PDE5 inhibition on human myofibroblast prostatic cells most likely via the activation of cGMP/protein kinase signaling [22].

However, clinical studies have not yet specifically investigated the role of PDE5Is in men with LUTS and prostatic inflammation despite the supporting preclinical evidence.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

The primary mechanism of action of NSAIDs is the inhibition of the activity of cyclooxygenase enzymes (COX-1 and 2) in the arachidonic acid cascade resulting in reduction of prostaglandin levels. COX-1 and 2 are expressed in human BPH tissue [23]. Elevated COX-2 expression has been associated with prostate growth through the increased synthesis of prostaglandins, which are important for the function and growth of smooth muscle cells and/or increased levels of the antiapoptotic Bcl-2 gene, which result in decrease in apoptosis of prostate tissue [23, 24]. In a preclinical study, ibuprofen a commonly used NSAID achieved a decrease in cell viability and induction of apoptosis in BPH cell lines [25]. Altavilla et al. [26] investigated the effects of flavocoxid, a dual inhibitor of the COX-2 and 5-lipoxygenase (5-LOX) in experimental BPH. Flavocoxid reduced prostate weight and hyperplasia, not only through the anti-inflammatory pathway, but also by promoting apoptosis.

Several studies investigated the clinical efficacy of NSAIDs either as monotherapy or in combination schemes on the management of LUTS. A meta-analysis of three

randomized controlled trials (RCTs) comparing NSAIDs (rofecoxib, celexocib, and tenoxicam) with placebo or other BPH medical treatment has recently published (Table 1). In total 183 men with LUTS due to BPH, were treated with NSAIDs for a period of 4–24 weeks [27]. A significant improvement in International Prostate Symptom Score (weighted mean difference (WMD) −2.89) and a marginal but statistically significant increase in peak urine flow (WMD 0.89 mL/s) was found. Interestingly, a relatively favorable safety profile with no withdrawals due to adverse events was reported [27]. NSAID (diclofenac 50 mg) was also tested for the management of nocturia secondary to nocturnal polyuria in a small, prospective, randomized, double-blind, placebo-controlled crossover study [28]. The mean number of nocturnal voids decreased from 2.8 to 2.3 and 2.7 voids with diclofenac and placebo, respectively ($p < 0.004$ between treatments). Diclofenac also significantly decreased the mean nighttime-to-daytime diuresis ratio compared to placebo.

Another study investigated the efficacy and safety of flurbiprofen, another COX-2 inhibitor, and alfuzosin, both alone and in combination on LUTS treatment [29]. After 4 weeks, IPSS and post void residual have been decreased significantly in all groups. However, Qmax have been improved only in the combination group.

Despite the promising results of the existing studies in terms of efficacy and safety, the main drawback is the short follow-up especially when taking into account the concerns regarding the long-term use of NSAIDs, such as the side-effect profile and possible comorbidities in renal and cardiovascular function.

Based on the above findings one could expect that use of NSAIDs would prevent or delay development of clinical BPH. However, there is conflicting data regarding the association of NSAIDs use and risk of BPH. In a cohort study, Schenk et al. [30] examined the impact of NSAIDs on incident BPH, using data from 4735 men without BPH at baseline in the placebo arm of the Prostate Cancer Prevention Trial. No evidence was found that NSAIDs were associated with the risk of BPH. Surprisingly, other studies have reported an increased risk of BPH in men taking NSAIDs [31, 32]. Recently, a population-based cohort of 74,754 Finnish men without BPH at baseline was analyzed. During the follow-up, NSAID users had a higher risk of incident BPH compared to nonusers. The observed risk correlated with duration of NSAID usage although the risk increase was recorded at short-term and low-dosage use [33].

Vitamin D3 receptor analogs (VDRAs)

Prostate stromal cells express the vitamin D receptor (VDR) that is upregulated by exposure to inflammatory stimuli [34]. Elocalcitol is a synthetic derivative of vitamin D3 that regulates cell proliferation and apoptosis via its binding to the VDR. Preclinical data showed that elocalcitol decreases stromal cells proliferation by targeting the activity of intraprostatic growth factors downstream of the androgen receptor and inhibits production of pro-inflammatory cytokines and chemokines in human BPH cells [35].

The effectiveness of elocalcitol in BOO has been studied in rats receiving a daily treatment (150 μg/kg) for 14 days. Elocalcitol did not prevent bladder hypertrophy but reduced the contractility of the detrusor muscle in the obstructed rats, as a result of the increased bladder weight [36]. In the clinical level, a phase II, randomized, placebo-controlled study included 119 patients with BPH. They received either BXL628 150 mcg/day or placebo for 12 weeks. The outcome revealed a statistically significant reduction in prostate volume (overall estimated treatment difference −7.22%) for the group of elocalcitol compared to placebo but not a significant difference in LUTS and Qmax [37]. The efficacy of three different therapeutic regimens of elocalcitol in terms of IPSS, Qmax, and reduction of prostate volume was evaluated after 6 months treatment. Elocalcitol 150 μg/day was identified as the optimal dose that achieved a statistically significant reduction in prostate volume and improvement in Qmax and IPSS compared to placebo [38]. However, despite evidence suggesting VDRs as potential therapeutic target for BPH/LUTS, no VDRAs are currently available.

Plant extracts—phytotherapy

Over the last 20 years, phytotherapy has been used for the management of male LUTS and almost 30 different plant extracts have been described [39]. In vitro, plant extracts can have anti-inflammatory, anti-androgenic and estrogenic effects, pro-apoptotic properties, and placebo effect [39]. However, not all these phytotherapeutic agents have been studied at the same level and represent a heterogeneous group with various extraction techniques and different concentrations of the active ingredients. Therefore, results even from meta-analyses should be interpreted with caution and comparisons cannot be made. Currently, the 2017 European Association of Urology Guidelines on non-neurogenic male LUTS have not made any specific recommendations on phytotherapy for the treatment of male LUTS due to product heterogeneity, a limited regulatory framework, and methodological limitations of the published trials and meta-analyses [2].

Serenoa repens is the most common plant extract used for the management of male LUTS. Many different extracts are available, but the hexanic lipidosterolic extract of Serenoa repens (HESr) has been extensively studied in both basic and clinical research. With regard to its

anti-inflammatory effect, HESr was found to act at different sites in the arachidonic acid cascade by inhibiting prostaglandin synthesis (via blockade of the activity of phospholipase A2 extract) and by inhibiting the production of 5-LOX metabolites of arachidonic acid [40]. HESr can modify inflammation status by decreasing infiltrates of B lymphocytes, IL-1b, and TNF-a, increasing the expression of anti-inflammatory genes and decreasing the expression of pro-inflammatory genes [40]. It has been shown also to inhibit early steps of leukocyte infiltration by down-regulating monocyte chemotactic protein-1/C-C motif chemokine ligand 2 (MCP-1/CCL2) and vascular cell adhesion molecule-1 (VCAM-1) expression in human prostate and vascular cells in an inflammatory environment [41].

In a multicenter clinical, patients with BPH were randomized to receive either HESr 160 mg for 3 months before surgery (transurethral resection of the prostate or adenomectomy) or no treatment [42]. Tissue samples taken at the time of surgery were analyzed for infiltrates and inflammatory markers (CD-3, CD-20, and CD-68) and for histologic aspects of inflammation. A correlation was found between a significant reduction in B lymphocytes and IL-1b and TNF-a levels and a significant improvement in IPSS clinical symptoms in patients treated with HESr [42].

A RCT with 209 patients receiving either HESr 320 mg/day or tamsulosin 0.4 mg for 3 months investigated the anti-inflammatory properties of HESr [43]. Urine stream was collected after digital rectal examination and mRNA was extracted from prostatic epithelial cells at baseline and after 3 months. MCP-1/CCL2, interferon γ-induced protein 10/C-X-C motif chemokine 10 and macrophage migration inhibitory factor (MIF) were detected at baseline and significantly reduced in the group of heSR after 3 months of treatment. A subgroup analysis showed a higher decrease in IPSS in patients treated with HESr and MIF over-expression at baseline than those who did not over-express MIF [43]. These results suggest that inflammation biomarkers may identify those patients who will benefit most from treatment with HESr.

An updated Cochrane report reviewed 30 RCTs comprising 5222 men on all the available preparations of Serenoa repens [44]. Mean follow-up ranged from 4 to 60 weeks. It was concluded that Serenoa repens was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Qmax, or prostate size reduction. However, the similar improvement in IPSS or Qmax compared with finasteride or tamsulosin might be interpreted as treatment equivalence. A very recent systematic review analyzed only the available RCTs on the efficacy and safety of HESr [45]. It was found that HESr was effective for improving urinary symptoms and urinary flow in men with prostatic enlargement compared with placebo (Table 1). The systematic review also confirmed that HESr had a comparable to tamsulosin and short-term finasteride in symptoms improvement. This recent analysis indicates the heterogeneity in the biological activity of the phytotherapeutic agents even if they come from the same plant. Therefore, it is reasonable that a single recommendation for all the available phytotherapeutic agents cannot be made and a recommendation should be given for each specific product with the same validated extraction technique and/or content in active principles.

Statins

Statins are commonly used to treat dyslipidemia, aiming to decrease the cardiovascular disease. They can also reduce bladder and prostatic fibrosis through modulation of expression of connective tissue growth factor, increased apoptosis/reduced proliferation of prostatic epithelium and stroma and improved blood flow to the LUT [46]. Moreover, statins can decrease prostate weight, disrupt the ultramicroscopic structure of prostatic tissue and lower the serum levels of IL-6 and IGF-1 in in vivo models. In a preliminary phase 2, randomized, placebo-controlled trial on the use of statin for the treatment of LUTS/BPH, atorvastatin 80 mg for 26 weeks was not effective in symptoms reduction, decrease of prostate volume or improvement of Qmax [47].

However, in an RCT on 791 patients with BPH, 1 year of statin plus α-blocker administration significantly reduced PSA and prostate volume compare to those treated with α-blockers alone [48].

In a recently published RCT on 135 men treated with simvastatin, atorvastatin, or placebo for 1 year, the use of statins reduces the levels of serum total cholesterol and triglycerides, IL-6, IPSS, and prostate volume. Interestingly, the reduction in prostate volume was directly related to the reduction of triglyceride and IL-6 and the increase of HDL-cholesterol [49]. Hence, the reduction of prostate inflammation, due to the control of dyslipidemia, could represent a therapeutic option for men with LUTS/BPH and MetS.

Conclusions

Research has focused on the understanding of the underlying pathophysiological mechanisms and natural history of LUTS due to BPO. Prostatic inflammation seems to play an essential role in the development of BPH and could be a treatment target for the management of male LUTS. The present narrative review shows that there are several drugs classes under investigation but there is a wide variation in the degree of mature of each therapy. Some molecules have proved their efficacy in preclinical studies but confirmation and further evaluation in humans are required. Other drugs

have been assessed in clinical studies but they still have a long way to go before they can be adopted in clinical practice. On the other hand, drugs like tadalafil or Serenoa repens have been used in clinical practice but it has not been clearly understood if their efficacy is thank and to what extent to their anti-inflammatory properties since several mechanisms of action have been proposed. In addition, lifestyle changes should be advised to patients with male LUTS.

The data reported further support the rationale for investigating agents that may alter and improve the inflammatory environment in the prostate. Robust data coming from high-quality studies with long-term follow-up are still needed to decide about the position of the new drugs since safety and durability are also important parameters. It is our knowledge that LUTS pathogenesis is multifactorial; therefore, the next reasonable research steps should include the combination of established medical treatments and emerging new drug classes. Trials investigating the efficacy and safety of a-blockers (or 5aRIs) with drugs with anti-inflammatory properties should be our next priority. In the future, the most important and critical research direction should be the identification of biomarkers clinical (such as MetS) and/or molecular that will indicate the status of prostatic inflammation involvement in each individual patient with LUTS. This will allow optimal patients selection and tailoring of treatment in order to achieve maximal efficacy.

The quest for the "holy grail" of optimal medical treatment of male LUTS continues.

Compliance with ethical standards

Conflict of interest A.d.l.T.: Astellas, Bouchara-Recordati, GSK, Pierre Fabre Medicament. S.G.: Astellas, Angelini Pharma Hellas, GSK, Lilly, Pierre Fabre Medicament. M.G.: Astellas, Bayer, GSK, Ibsa, Konpharma, Lilly, Pierre Fabre Medicament, Pfizer. M.S. declares no conflict of interest.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61:37–49.
2. Gravas S, Bach T, Drake M, Gacci M, Gratzke C, Herrmann TRW, et al. Guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO). http://uroweb.org/wp-content/uploads/EAU-Guidelines-Management-of-non-neurogenic-male-LUTS-2016.pdf. Accessed 15 Nov 2017.
3. Chapple CR, Wein AJ, Abrams P, Dmochowski RR, Giuliano F, Kaplan SA, et al. Lower urinary tract symptoms revisited: a broader clinical perspective. Eur Urol. 2008;54:563–9.
4. Robert G, Descazeaud A, Allory Y, Vacherot F, de la Taille A. Should we investigate prostatic inflammation for the management of benign prostatic hyperplasia? Eur Urol Suppl. 2009;8:879–86.
5. Schatteman PH, Hoekx L, Wyndaele JJ, Jeuris W, Van Marck E. Inflammation in prostate biopsies of men without prostatic malignancy or clinical prostatitis: correlation with total serum PSA and PSA density. Eur Urol. 2000;37:404–12.
6. Di Silverio F, Gentile V, De Matteis A, Mariotti G, Giuseppe V, Luigi PA, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. Eur Urol. 2003;43:164–75.
7. Nickel JC. Inflammation and benign prostatic hyperplasia. Urol Clin North Am. 2008;35:109–15.
8. De Nunzio C, Kramer G, Marberger M, Montironi R, Nelson W, Schröder F, et al. The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. Eur Urol. 2011;60:106–17.
9. Wang L, Yang JR, Yang LY, Liu ZT. Chronic inflammation in benign prostatic hyperplasia: implications for therapy. Med Hypotheses. 2008;70:1021–3.
10. Kramer G, Mitteregger D, Marberger M. Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? Eur Urol. 2007;51:1202–16.
11. Taoka R, Tsukuda F, Ishikawa M, Haba R, Kakehi Y. Association of prostatic inflammation with down-regulation of macrophage inhibitory cytokine-1 gene in symptomatic benign prostatic hyperplasia. J Urol. 2004;171:2330–5.
12. Russo GI, Cimino S, Castelli T, Favilla V, Gacci M, Carini M, et al. Benign prostatic hyperplasia, metabolic syndrome and non-alcoholic fatty liver disease: is metaflammation the link? Prostate. 2016;76:1528–35.
13. Gacci M, Sebastianelli A, Salvi M, De Nunzio C, Vignozzi L, Corona G, et al. Benign prostatic enlargement can be influenced by metabolic profile: results of a multicenter prospective study. BMC Urol. 2017;17:22.
14. Vignozzi L, Gacci M, Cellai I, Santi R, Corona G, Morelli A, et al. Fat boosts, while androgen receptor activation counteracts, BPH-associated prostate inflammation. Prostate. 2013;73:789–800.
15. Gacci M, Vignozzi L, Sebastianelli A, Salvi M, Giannessi C, De Nunzio C, et al. Metabolic syndrome and lower urinary tract symptoms: the role of inflammation. Prostate Cancer Prostatic Dis. 2013;16:101–6.
16. De Nunzio C, Brassetti A, Gacci M, Finazzi Agrò E, Carini M, Presicce F, et al. Patients with prostatic inflammation undergoing transurethral prostatic resection have a larger early improvement of storage symptoms. Urology. 2015;86:359–65.
17. Parsons JK, Kashefi C. Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms. Eur Urol. 2008;53:1228–35.
18. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al. Intensive lifestyle changes may affect the progression of prostate cancer. J Urol. 2005;174:1065–9.
19. Gacci M, Andersson KE, Chapple C, Maggi M, Mirone V, Oelke M, et al. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol. 2016;70:124–33.
20. Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol. 2012;61:994–1003.
21. Morelli A, Comeglio P, Filippi S, Sarchielli E, Vignozzi L, Maneschi E, et al. Mechanism of action of phosphodiesterase type 5 inhibition in metabolic syndrome-associated prostate alterations: an experimental study in the rabbit. Prostate. 2013;73:428–41.
22. Vignozzi L, Gacci M, Cellai I, Morelli A, Maneschi E, Comeglio P, et al. PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. Prostate. 2013;73:1391–402.

23. Kirschenbaum A, Klausner AP, Lee R, Unger P, Yao S, Liu XH, et al. Expression of cyclooxygenase-1 and cyclooxygenase-2 in the human prostate. Urology. 2000;56:671–6.
24. Wang W, Bergh A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. Prostate. 2004;61:60–72.
25. Minnery CH, Getzenberg RH. Benign prostatic hyperplasia cell line viability and modulation of JM-27 by doxazosin and ibuprofen. J Urol. 2005;174:375–9.
26. Altavilla D, Minutoli L, Polito F, Irrera N, Arena S, Magno C, et al. Effects of flavocoxid, a dual inhibitor of COX and 5-lipoxygenase enzymes, on benign prostatic hyperplasia. Br J Pharmacol. 2012;167:95–108.
27. Kahokehr A, Vather R, Nixon A, Hill AG. Non-steroidal anti-inflammatory drugs for lower urinary tract symptoms in benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials. BJU Int. 2013;111:304–11.
28. Addla SK, Adeyoju AB, Neilson D, O'Reilly P. Diclofenac for treatment of nocturia caused by nocturnal polyuria: a prospective, randomized, double-blind, placebo-controlled crossover study. Eur Urol. 2006;49:720–6.
29. Gokkaya GS, Aktas BK, Ozden C, Bulut S, Karabakan M, Erkmen AE, et al. Flurbiprofen alone and in combination with alfuzosin for the management of lower urinary tract symptoms. Cent Eur J Urol. 2015;68:51–56.
30. Schenk M, Calip GS, Tangen CM, Goodman P, Parsons JK, Thompson IM, et al. Indications for and use of nonsteroidal antiinflammatory drugs and the risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. Am J Epidemiol. 2012;176:156–63.
31. Meigs JB, Mohr B, Barry MJ, Collins MM, McKinlay JB. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. J Clin Epidemiol. 2001;54:935–44.
32. Kang D, Andriole GL, van de Vooren RC, Crawford D, Chia D, Urban DA, et al. Risk behaviours and benign prostatic hyperplasia. BJU Int. 2004;93:1241–5.
33. Nygård LH, Talala K, Taari K, Tammela TLJ, Auvinen A, Murtola TJ. The effect of non-steroidal anti-inflammatory drugs on risk of benign prostatic hyperplasia. Prostate. 2017;77:1029–35.
34. Fibbi B, Penna G, Morelli A, Adorini L, Maggi M. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. Int J Androl. 2010;33:475–88.
35. Adorini L, Penna G, Amuchastegui S, Cossetti C, Aquilano F, Mariani R, et al. Inhibition of prostate growth and inflammation by the vitamin D receptor agonist BXL-628 (elocalcitol). J Steroid Biochem Mol Biol. 2007;103:689–93.
36. Schroder A, Colli E, Maggi M, Andersson KE. Effects of a vitamin D(3) analogue in a rat model of bladder outlet obstruction. BJU Int. 2006;98:637–42.
37. Colli E, Rigatti P, Montorsi F, Artibani W, Petta S, Mondaini N, et al. BXL628, a novel vitamin D3 analog arrests prostate growth in patients with benign prostatic hyperplasia: a randomized clinical trial. Eur Urol. 2006;49:82–86.
38. Montorsi F, Colli E. Elocalcitol in the treatment of BPH: a multicenter, randomized, placebo-controlled phase IIb clinical trial. J Urol. 2008;179(Suppl):700–1. (abstract 2035)
39. Keehn A, Lowe FC. Complementary and alternative medications for benign prostatic hyperplasia. Can J Urol. 2015;22(Suppl 1): 18–23.
40. de la Taille A. Therapeutic approach: the importance of controlling prostatic inflammation. Eur Urol Suppl. 2013;12:116–23.
41. Latil A, Libon C, Templier M, Junquero D, Lantoine-Adam F, Nguyen T. Hexanic lipidosterolic extract of Serenoa repens inhibits the expression of two key inflammatory mediators, MCP-1/CCL2 and VCAM-1, in vitro. BJU Int. 2012;110: 301–7.
42. Vela Navarrete R, Garcia Cardoso JV, Barat A, Manzarbeitia F, López Farré A. BPH and inflammation: pharmacological effects of permixon on histological and molecular inflammatory markers. Results of a double blind pilot clinical assay. Eur Urol. 2003;44:549–55.
43. Latil A, Pétrissans MT, Rouquet J, Robert G, de la Taille A. Effects of hexanic extract of Serenoa repens (permixon® 160 mg) on inflammation biomarkers in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. Prostate. 2015;75:1857–67.
44. Tacklind J, Macdonald R, Rutks I, Stanke JU, Wilt TJ. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2012;12:CD001423.
45. Novara G, Giannarini G, Alcaraz A, Cózar-Olmo JM, Descazeaud A, Montorsi F, et al. Efficacy and safety of hexanic lipidosterolic extract of Serenoa repens (permixon) in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials. Eur Urol Focus. 2016;2:553–61.
46. Mills IW, Crossland A, Patel A, Ramonas H. Atorvastatin treatment for men with lower urinary tract symptoms and benign prostatic enlargement. Eur Urol. 2007;52:503–9.
47. Zhang X, Shen F, Dong L, Zhao X, Qu X. Influence and pathophysiological mechanisms of simvastatin on prostatic hyperplasia in spontaneously hypertensive rats. Urol Int. 2013;91:467–73.
48. Lee SH, Park TJ, Bae MH, Choi SH, Cho YS, Joo KJ, et al. Impact of treatment with statins on prostate-specific antigen and prostate volume in patients with benign prostatic hyperplasia. Korean J Urol. 2013;54:750–5.
49. Zhang X, Zeng X, Dong L, Zhao X, Qu X. The effects of statins on benign prostatic hyperplasia in elderly patients with metabolic syndrome. World J Urol. 2015;33:2071–7.