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Why and How to Evaluate Chronic Prostatic Inflammation

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Abstract

Context: In recent years, increasing scientific evidence has emerged to show that prostatic inflammation is one of the key predictive factors for benign prostatic hyperplasia (BPH).
Objective: This review describes the recent literature regarding the relationship between prostatic inflammation and BPH, and focuses on the clinical perspective of why and how to evaluate prostatic inflammation.
Evidence acquisition: Published literature relating to the role and evaluation of prostatic inflammation in BPH was identified by searching PubMed (Medline).
Evidence synthesis: Laboratory and clinical studies have demonstrated that prostatic inflammation is a central and relevant mechanism in prostate enlargement and BPH development. Despite the potential clinical use of predictive biomarkers such as interleukin-8, monocyte chemotactic protein-1, chemokine (C-C motif) receptor 7, cytotoxic T lymphocyte-associated antigen 4, inducible T-cell costimulator, and CD40 ligand, biopsy remains the standard procedure for evaluating prostatic inflammation histologically; however, biopsy can only be performed in patients with suspected prostate cancer. In the absence of biopsy data, prostatic calcification and symptom severity can assist clinicians in diagnosing suspected prostatic inflammation. Prostatic calcification has been shown to be present in 86% of symptomatic male patients aged >50 yr. Clinical data have also demonstrated that chronic inflammation and International Prostate Symptom Score are statistically significantly correlated, with storage symptoms being particularly strongly correlated with chronic inflammatory status. Furthermore, as the presence of metabolic syndrome has been shown to be highly correlated with lower urinary tract symptoms (LUTS) due to BPH (LUTS/BPH), clinicians need to consider metabolic syndrome accompanying chronic prostatic inflammation when evaluating patients for LUTS/BPH.
Conclusions: Chronic prostatic inflammation plays a central role in the pathogenesis and progression of BPH; therefore, it is important to evaluate it appropriately in patients with LUTS/BPH or suspected prostate cancer.

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1. Introduction

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) represent the most common urologic disorders among elderly men, predominantly affecting men aged >50 yr [1]. Based on an increasing body of evidence from in vitro, in vivo, and clinical studies, inflammation is now considered to play a central and relevant role in the pathogenesis and development of BPH. Therefore, chronic inflammation could represent a potential

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new target for medical therapy of LUTS due to BPH (LUTS/BPH) [2]. Interestingly, this silent, persistent inflammatory status in the prostate gland must be distinguished from the clinical condition characterizing chronic prostatitis.

The purpose of this literature review is to critically analyze the evidence concerning the relationship between chronic prostatic inflammation and BPH/LUTS and to discuss why and how to identify patients with chronic prostatic inflammation.

2. Evidence acquisition

Publications relating to the role of inflammation in BPH were identified by searching the PubMed Medline database. Search terms included *benign prostatic hyperplasia (BPH)*, *inflammation*, *biomarkers*, *biopsy*, and *prostatic calcification*.

Additional studies were identified from the reference sections of selected papers. Although English language was not a specific search parameter, publications were limited to those in English. The Medline search was limited to the past decade. Publications presented in this review were selected because they were the most relevant in supporting the reasons why and how to evaluate chronic prostatic inflammation in patients with LUTS/BPH.

3. Evidence synthesis

3.1. Prostatic inflammation

Although aging represents the most significant risk factor for the development of BPH and LUTS, several other mechanisms have been proposed to be involved in the pathogenesis and progression of BPH. Hormonal alterations as well as insulin resistance with secondary hyperinsulinemia and increased sympathetic nerve activity have also been proposed. Moreover, in the last few years, the role of prostatic inflammation as a crucial part of BPH pathogenesis and progression has emerged. It has been hypothesized that inflammatory infiltrate leads to tissue damage and to a chronic process of wound healing that might subsequently determine prostatic enlargement [3].

T cells represent the major component of the inflammatory infiltrate observed within the prostatic gland. Moreover, an increased expression of B lymphocytes and macrophages was reported. These antigen-presenting cells play an important role in the activation of T lymphocytes and in the subsequent onset of an inflammatory state [4].

The chronic inflammatory condition may contribute to tissue injury, activating the release of cytokines and increasing the concentration of growth factors, thus creating a local vicious cycle. In this context, the upregulation of proinflammatory cytokines has been widely reported in prostatic tissues of patients affected by BPH. Interestingly, interleukin (IL)-8 has been proposed as a link between chronic prostatic inflammation and the development of BPH. Indeed, this cytokine is produced by epithelial prostate cells and can induce the expression of fibroblast growth factor (FGF)-2, a potent stromal and epithelial growth factor, and consequently promote the abnormal proliferation of prostatic cells. Finally, local hypoxia induced by chronic inflammation may also play a role in the pathophysiology of BPH. Indeed, it induces the release of reactive oxygen species, which can promote neovascularization and the release of vascular endothelial growth factors (VEGFs; ie, VEGF, IL-8, FGF-7, transforming growth factor [TGF]-β, and FGF-2). These growth factors may interact not only with inflammatory cells, but also with the stromal and epithelial cells of the prostate, leading to prostatic enlargement [3].

3.2. How do we evaluate prostatic inflammation?

The histologic diagnosis of chronic prostatic inflammation can only be performed in patients who have undergone a prostate biopsy for suspected prostate cancer. In these cases, the presence of chronic prostatic inflammation can be the conclusive diagnosis or it can be associated with other findings, including a positive diagnosis of prostate cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, or BPH. Interestingly, Irani et al. proposed classifying prostatic inflammation on the basis of a hypothetical histologic grading related to the extension of inflammatory cells. Moreover, a histologic aggressiveness grading system, based on the effect that these inflammatory cells produce on prostate tissue, has been described [5]. Specifically, histologic grading can be classified as grade 0, no inflammation; grade 1, scattered inflammatory cell infiltrate without nodules; grade 2, no confluent lymphoid nodules; and grade 3, large inflammatory areas with confluence. Similarly, histologic aggressiveness can be subdivided into grade 0, no contact between inflammatory cells and glandular epithelium; grade 1, contact between inflammation and epithelium; grade 2, interstitial infiltrate with glandular disruption; and grade 3, glandular epithelical disruption on >25% of the examined material [6]. Unfortunately, many uropathologists failed to use previous specific terminology to describe the presence of chronic inflammation in prostate biopsy specimens. Thus, the importance of histologic grading and aggressiveness of chronic prostatic inflammation on prostate biopsy must be shared with pathologists.

The prevalence of chronic prostatic inflammation in patients with LUTS/BPH has been estimated in the context of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial [7]. 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 [8]. 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.

Biomarkers represent a potential noninvasive alternative to prostate biopsy in the detection of chronic prostatic inflammation. Prostate tissue often contains increased inflammatory infiltrates, including T cells and macrophages.

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Cytokines are not only key mediators of inflammation but may also play an important role in the initiation and progression of BPH. Thus, a number of proinflammatory cytokines have potential application as predictive biomarkers. Currently, the potential role of biomarkers that are present in seminal plasma, serum, urine, or prostatic secretion is not clearly defined. The presence of IL-8 in seminal plasma has been proposed as a promising predictive biomarker of chronic prostatic inflammation [9,10]. IL-8 is a proinflammatory cytokine that is produced by prostate epithelial cells. It directly promotes BPH stromal cell proliferation in an autocrine/paracrine manner and represents a potential link between chronic inflammation and the subsequent development of BPH [9,10]. However, despite these initial positive findings, more studies are required to further define the potential role of IL-8 as a predictive biomarker for prostatic inflammation and its application in clinical practice.

Monocyte chemotactic protein-1 (MCP-1), which appears to originate in prostatic stromal cells, represents another potential biomarker for prostatic inflammation. In prostatic secretion, MCP-1 levels have been shown to positively correlate with prostate volume and with mRNA levels of the macrophage marker CD68 [11]. Furthermore, MCP-1 levels in expressed prostatic secretion are easily assessable using enzyme-linked immunosorbent assay (ELISA) methods.

Urinary biomarkers, including chemokine (C-C motif) receptor 7 (CCR7), cytotoxic T lymphocyte-associated antigen (CTLA4), inducible T-cell costimulator (ICOS), and CD40 ligand (CD40LG), represent other potential candidates for detecting prostatic inflammation. Each of these urinary biomarkers has been shown to be upregulated at the mRNA level in patients with chronic prostatic inflammation [12]. CCR7 is a member of the G protein-coupled receptor family; it controls the migration of memory T cells to inflamed tissues and stimulates dendritic cell maturation. CTLA4, together with ICOS, belongs to the same family of cell-surface T-cell receptors, which is important for cell signaling, immune response, and cell proliferation. After being expressed, CTLA4 and ICOS are released in soluble form and are present in high concentrations in urine samples, as readily measured using conventional ELISA procedures. ICOS is significantly associated with clinical parameters such as maximum uroflowmetry and postvoid residual. CD40LG is a protein that is expressed on the surface of T cells and is a regulator of B-cell function by ligating CD40; CD40LG has been shown to be expressed on the surface of prostatic epithelial cells [12].

However, as noted previously, more robust evidence from prospective clinical studies is required before predictive biomarkers are potentially introduced into routine clinical practice to assist in the diagnosis and surveillance of chronic prostatic inflammation.

3.3. Signs and symptoms of suspected chronic prostatic inflammation

A number of factors, including prostatic calcification and symptom severity, can assist the clinician in suspecting the presence of chronic prostatic inflammation.

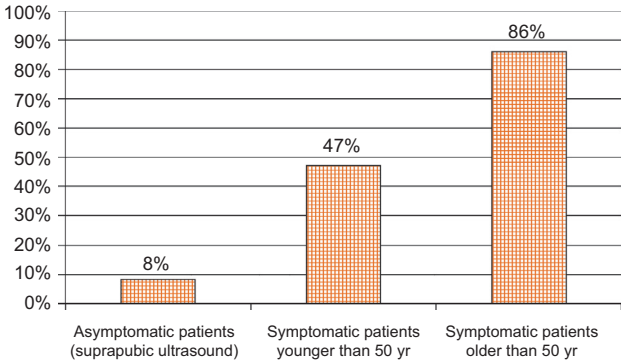

Fig. 1 – The prevalence of prostatic calcification [14,15].

3.3.1. *Prostatic calcifications*

Abdominal and pelvic ultrasound with or without transrectal prostate ultrasound are currently considered in the diagnostic assessment of patients with LUTS/BPH [13]. Thus, the presence of prostatic calcifications is very simple to detect during the patient work-up process. Whilst some small prostate calcifications can be considered a normal, incidental ultrasound finding, larger or multiple prostatic calculi may represent an indirect sign of a persistent inflammatory status that requires further investigation [14]. Interestingly, the prevalence of prostatic calcifications varies depending on whether patients are asymptomatic, or symptomatic and aged <50 yr or>50 yr (Fig. 1), with 86% of prostatic calcifications in symptomatic patients aged >50 yr [14,15]. This age-related difference in prevalence may be explained by different etiologic mechanisms of prostatic calcifications (Fig. 2). Prostatic calcifications leading to obstruction of intraprostatic ducts and inflammatory response to prostatic disease result from alterations in prostatic fluid. In younger men, prostatic fluid alterations are often due to infections or inflammatory prostatic disease (eg, prostatitis) [16]. Conversely, in older men, prostatic fluid alterations generally reflect an age-related alteration [17]. A study evaluating 604 men aged ≥40 yr (mean: 54.6 yr) who had a transrectal prostate ultrasound as part of a standard health check-up showed that the

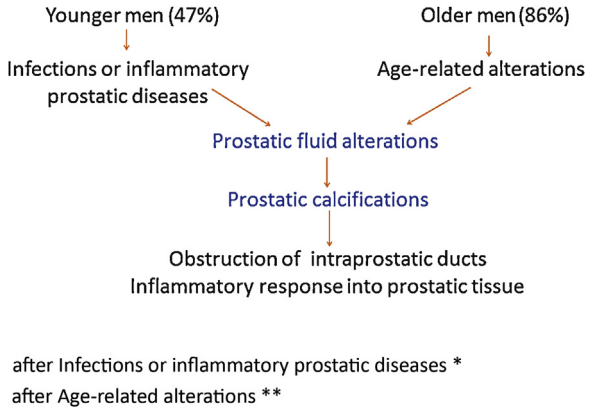

Fig. 2 – Prostatic calcifications: etiologic mechanisms. * Shoskes et al. [16]. ** Untergasser et al. [17].

presence of prostatic calcification was correlated with a significantly worse International Prostate Symptom Score (IPSS), quality of life (QoL), storage, voiding symptoms, and maximum urine flow [18]. Moreover, moderate/marked prostatic calcifications turned out to be an independent risk predictor for moderate to severe LUTS (odds ratio, 1.68; $p = 0.02$) [18].

The presence of an important self-perpetuating mechanistic process was hypothesized that is likely to be involved in prostatic calcifications resulting from age-related prostatic fluid alterations and the subsequent prostatic tissue inflammatory response (Fig. 3) [19]. Gandaglia et al. [3] showed that one concomitant factor or more, including bacterial/viral infections, sexually transmitted disease, dietary factors, hormones, autoimmune response, and urine reflux, can promote chronic prostatic inflammation. The inflammatory reaction is characterized by T lymphocyte infiltration, proinflammatory cytokine activation and upregulation, increased expression of stromal and epithelial growth factors (eg, fibroblast growth factor), and subsequent abnormal prostate cell proliferation. Other factors that play an important role in the inflammatory process include local hypoxia, neovascularization, and additional growth factor production [3].

3.3.2. *Symptom severity*

A post hoc analysis of the REDUCE trial showed a statistically significant correlation between chronic prostatic inflammation (average and maximum chronic inflammation) and total, irritative, and obstructive IPSS scores [8]. Conversely, no correlation between acute inflammation (average and maximum) and IPSS scores was documented. From the statistical perspective, the correlation with chronic inflammation was stronger with regard to storage symptoms, indicating a more relevant correlation between storage symptoms and chronic inflammatory prostatic status. These findings have been confirmed in two subsequent clinical studies [20,21]. Robert et al. highlighted in detail that IPSS score and prostate volume were significantly ($p = 0.02$) higher in patients with high-grade prostatic inflammation in comparison with those having low-grade inflammation [20].

In a study by Kwon and colleagues [21], 82 patients underwent transrectal ultrasound-guided needle prostate biopsy and were stratified according to the presence of either low-grade or high-grade chronic inflammation. Between-group comparisons with regard to IPSS and QoL were conducted at baseline, 1, 3, 6, and 12 mo after treatment for BPH (α-blockers and 5α-reductase inhibitors [5-ARIs]). Patients with high-grade chronic inflammation reported significantly lower changes in IPSS and storage symptom scores over the 12-mo follow-up period compared with patients with low-grade inflammation. Patients with low-grade inflammation demonstrated continuous improvement of storage symptoms until 12 mo; however, those in the high-grade group only showed improvement until 3 mo. Maximal QoL improvements were observed at 6 mo in the high-grade inflammation group and at 3 mo in the low-grade group. In addition, there was no episode of surgery in the low-grade group, but four patients (9.1%) in the high-grade group underwent transurethral resection

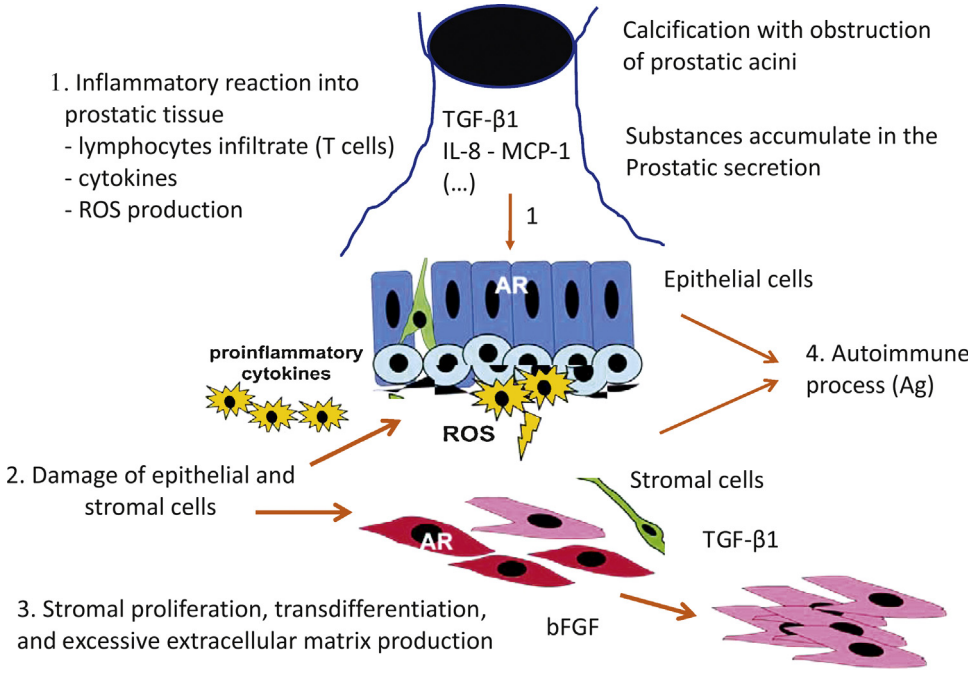

Fig. 3 – Schematic representation of the mechanisms responsible for the process of prostatic inflammation. Prostatic obstruction results in the accumulation of inflammatory substances in prostatic secretions that stimulate an inflammatory reaction in prostatic tissue. Subsequent steps are involved in the damage of epithelial and stromal cells caused by the inflammatory and healing processes characterized by stromal proliferation and excessive extracellular matrix production. Reproduced with permission from John Wiley & Sons [19]. ROS = reactive oxygen species; TGF-β1 = transforming growth factor β1; IL-8 = interleukin 8; MCP-1 = monocyte chemotactic protein 1; bFGF = basic fibroblast growth factor; Ag = antigen; AR = autoimmune response.

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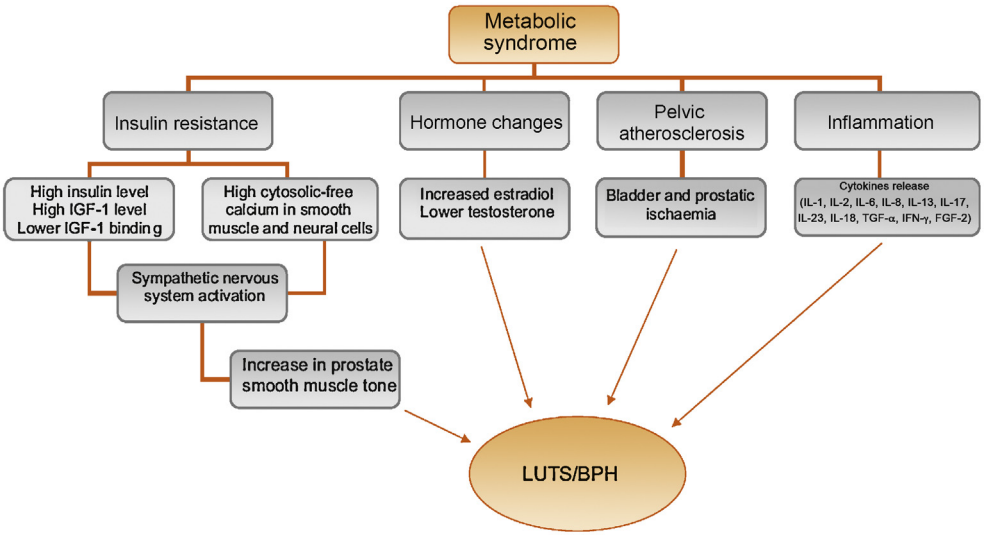

Fig. 4 – The proposed link between chronic inflammation and metabolic syndrome. Reproduced with permission from Elsevier [22]. IGF = insulin-like growth factor; IL = interleukin; TGF = tumor growth factor; IFN = interferon; FGF = fibroblast growth factor; LUTS/BPH = lower urinary tract symptoms due to benign prostatic hyperplasia.

of the prostate due to acute urinary retention or insufficient therapeutic response [21].

These data indicate that in patients with high-grade inflammation, the use of α-blockers with or without 5-ARIs can be insufficient to reduce symptom severity. Therefore, new therapeutic options are needed to block the effects of chronic prostatic inflammation status.

In addition to previous signs and symptoms, clinicians can suspect the presence of persistent chronic prostatic inflammation 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 [22] (Fig. 4).

Gacci et al. analyzed 271 men with LUTS/BPH who underwent simple prostatectomy. More than 30% of enrolled patients had metabolic syndrome and this condition was shown to be positively associated with prostate volume, prostatic anterior–posterior diameter, and intraprostatic inflammatory score [23].

4. Conclusions

Chronic prostatic inflammation is involved in both the etiology and progression mechanisms of LUTS/BPH. The prevalence of this condition can be estimated at approximately 75% of patients with LUTS/BPH. The diagnosis can be done only in patients who undergo prostate biopsy for suspected prostate cancer. Conversely, in patients who are not candidates for prostate biopsy, the presence of chronic prostatic inflammation could be predicted via dosing biomarkers such as IL-8, MCP-1, CCR7, CTLA4, ICOS, or CD40LG. However, although a number of promising biomarkers have shown potential, further research is required before any of these biomarkers can be recommended for use in clinic practice.

Prostatic calcification and symptom severity (particularly in the presence of predominantly storage symptoms), in combination with ultrasound, can assist urologists to suspect the presence of a chronic prostatic inflammatory status. Finally, in patients with metabolic syndrome, chronic prostatic inflammation is a clinically relevant mechanism for LUTS/BPH. An improved understanding of the pathology, particularly with regard the inflammatory processes involved, could certainly allow for better management of BPH.

Conflicts of interest

V. Ficarra and G. Novara declare that they have received fees for serving as speakers and/or consultants for Astellas, Eli Lilly, Pierre Fabre, Recordati, and Takeda within the last 3 yr.

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