Benign Prostatic Hyperplasia and Its Aetiologies

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Abstract

Context: Benign prostatic hyperplasia (BPH) is a well-known condition characterised by prostate growth accompanied by lower urinary tract symptoms. Several mechanisms seem to be involved in the development and progression of BPH.

Objective: To review the most important findings regarding the key mechanisms involved in the pathophysiology of BPH.

Evidence acquisition: During the 2009 annual meeting of the European Association of Urology in Stockholm, Sweden, a satellite symposium was held on BPH and its treatment. This paper is based on one of the presentations at the symposium. A structured, comprehensive literature review was performed using data retrieved from recent review articles, original articles, and abstracts.

Evidence synthesis: Several mechanisms seem to be implicated in the pathophysiology of BPH. These represent age-related tissue modifications, hormonal alterations, and metabolic syndrome as well as inflammation. Although androgens do not cause BPH, the development of BPH requires the presence of androgens. Moreover, several studies support the association between noninsulin-dependent diabetes mellitus, hypertension, obesity, and low high-density lipoprotein cholesterol and the development of BPH. Finally, recent increasing evidence seems to support the idea that BPH consists of an inflammatory-based disorder. Inflammation would be initiated by an unknown stimulus that would create a proinflammatory milieu within the gland. This theory is confirmed by several basic research and clinical studies that showed a statistically significant association between inflammation and BPH severity and progression.

Conclusions: Although the pathogenesis of BPH is not yet fully understood, several mechanisms seem to be involved in the development and progression of the disease. These mainly include systemic and local hormonal and vascular alterations as well as prostatic inflammation that would stimulate cellular proliferation. Inflammation would be initiated by an unknown stimulus that would create a proinflammatory environment within the prostate. Therefore, from the recent clinical and basic research studies, a novel approach in the clinical management of BPH might focus on the inflammatory process involved in the development and progression of the disease.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a progressive condition characterised by prostate enlargement accompanied by lower urinary tract symptoms (LUTS) [1,2]. Benign prostatic hyperplasia arises in the periurethral and transition zones of the prostatic gland and represents an inescapable phenomenon for the ageing male population [3]. Although BPH is uncommon before age 40, roughly 50% of men develop BPH-related symptoms at 50 yr of age. The incidence of BPH increases by 10% per decade and reaches 80% at approximately 80 yr of age [4,5]. An estimated 75% of men >50 yr of age have symptoms arising from BPH, and 20–30% of men reaching 80 yr of age require surgical intervention for the management of BPH [1,2]. Despite the high impact of BPH on public health, however, the pathogenesis of BPH is still largely unresolved. Indeed, although multiple theories have been proposed, the aetiology of BPH still remains uncertain in some aspects. Several mechanisms seem to be involved in the development and progression of BPH. Although ageing represents the central mechanism implicated, recent novel findings also highlighted the key role of hormonal alterations, metabolic syndrome, and inflammation [3,6–12] (Fig. 1). The current paper reviews the most important findings regarding the key mechanisms involved in the pathophysiology of BPH.

2. Evidence acquisition

During the 2009 annual meeting of the European Association of Urology in Stockholm, Sweden, a satellite symposium was held on BPH and its treatment. This paper is based on one of the presentations at the symposium. A structured, comprehensive literature review was performed. Separate searches were done within the MEDLINE database and The Cochrane Library Central Search. The initial search terms were benign prostatic hyperplasia and physiopathology. Based on the results of these initial searches, additional separate searches were performed using the term benign prostatic hyperplasia in combination with metabolic syndrome, aging, inflammation, and hormonal alterations. Although English-language text was not a specific search parameter, only English-language publications were considered in the final assessment. Overall, 73 papers were selected, and they are included as references in this review article.

3. Evidence synthesis

3.1. Tissue remodelling in the ageing prostate

Ageing is the most significant risk factor for the development of BPH and the occurrence of LUTS [3,10–12]. Several studies have demonstrated a relationship between age and markers of BPH progression [13–16]. For instance, in the population-based Olmsted County study, moderate to severe urinary symptoms were recorded in 13% of men 40–49 yr of age versus 28% in subjects >70 yr [16]. Recently, Loeb et al. performed pelvic magnetic resonance imaging in 278 men without prostate cancer, and prostate volume measurements were assessed over time. The authors reported a median rate of prostatic volume change of 0.6 ml per year of age, corresponding to a median growth rate of 2.5% per year [17].

In ageing males, a significant tissue-remodelling process takes place within the prostate, especially in the transition zone (TZ). Interference in the delicate balance of interacting growth factor signalling pathways occurs, and stromal-epithelial interactions generate an increase in prostate volume. Specifically, the most significant modifications take place in the basal cells, which change their intracellular metabolism and become enlarged and hypertrophic. The development of BPH is also accompanied by the occurrence of corpora amylacea and prostatic calculi. These elements typically contain phosphate salts of calcium, magnesium, potassium, calcium carbonate, or calcium oxalate [18]. Subsequently, the altered secretions of luminal cells and the presence of corpora amylacea and prostatic calculi lead to further calcification, and clogged ducts become visible [19]. All of this tissue remodelling leads to alterations of highly specialised cell types responsible for tissue homeostasis and function.

Because cell growth is a consequence of either increased cell proliferation or decreased cell death, apoptotic activity was also suggested as a key cofactor in BPH development and progression. Although some authors reported similar levels of apoptosis in the epithelium of BPH relative to normal epithelium, other more recent reports have indicated that abnormal regulation of apoptosis may be associated with BPH [6–8]. Kiprianou et al examined the relative expression of two proteins involved in the regulation of prostate apoptosis: transforming growth factor (TGF)–β1 and Bcl-2, a potent apoptosis suppressor [7]. Analysis of the incidence of apoptosis in situ, using the
end-labelling terminal transferase staining technique for the detection of nucleosomal DNA fragmentation, revealed infrequent apoptotic staining in isolated basal and secretory prostate epithelial cells.

The authors also demonstrated that the apoptotic index of the secretory and basal cells of the prostate epithelium was higher in the normal prostate compared with BPH tissue, whereas there was a significant increase in the proliferative index of the respective cell populations in the hyperplastic prostate [7]. Balancing the apoptotic versus the proliferative activities revealed a substantial net decrease of apoptosis in both the glandular and basal epithelial cell compartments of the hypertrophic prostate when compared with the normal gland. Also TGF-β expression in the epithelial cells was found to be higher in BPH tissue compared with the normal prostate. Taken together, these results suggest a potential involvement of enhanced expression of antiapoptotic proteins in the deregulation of the normal apoptotic cell death mechanisms in the human prostate, thus resulting in a growth imbalance in favour of cell proliferation that might ultimately support hyperplasia. Subsequently, the induction of apoptosis and/or necrosis has become more and more appealing in the design and testing of novel therapies for prostatic diseases [6–8].

### 3.2. Hormonal alterations

Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty, and ageing. Studies on intraprostatic sex-steroid hormone levels have shown that bioavailable prostatic testosterone levels decline with age [20,21]. Luminal secretory cells require androgens, particularly the intracellular metabolite of testosterone, dihydrotestosterone (DHT), for terminal differentiation and secretory functions. DHT is predominantly generated by the prostatic 5α-reductase, which is present in fibroblasts of the stroma and in basal epithelial cells. In two interesting papers, Roberts et al reported higher DHT activity in BPH tissues [22,23]. Conversely, the proliferative index of the respective cell populations in BPH tissue relative to the adjacent normal prostate. Under-stading the mechanisms causing elevated androgen signalling may lead to a clarification of the role of DHT in the pathophysiology of BPH and potentially to the identification of novel approaches for its prevention and/or treatment.

Other studies have also assessed the role of estrogens in BPH. Circulating levels of free estradiol remain constant in the ageing man due to an age-related increase in body weight and adipose cells. Indeed, the prevalence of fat tissue is responsible for the expression of high levels of aromatase, which produces estrogen conversion [26]. The increased estrogenic stimulation of the prostate in the ageing man may lead to the reactivation of prostatic growth [27,28]. Estrogen-induced aberrations in prostate epithelial growth have also been observed in dogs, monkeys, and humans [29–31]. In addition to epithelial effects, estrogens also stimulate stromal cell proliferation [29–31]. Indeed, in vitro studies suggest that upregulation of estrogen receptor α in cultured prostate stromal cells is also associated with upregulation of fibroblast growth factor (FGF)-2 as well as other growth factors. Moreover, several studies demonstrated that the addition of androgens downregulated the estrogen receptor and various stroma-derived growth factors [32–34]. Finally, estrogen effects on the prostate gland may also be indirectly mediated through alterations in other serum hormones [35–37].

### 3.3. Metabolic syndrome

The association between metabolic syndrome and BPH has also been studied recently. Hammarsen et al were the first to demonstrate that noninsulin-dependent diabetes mellitus (NIDDM), hypertension, obesity, and low high-density lipoprotein cholesterol (HDL-C) levels constitute risk factors for the development of BPH [38,39]. In a Swedish study of 250 patients with BPH, the authors reported a median annual BPH growth rate of 1.04 ml/yr. Men with fast-growing BPH had a higher prevalence of NIDDM (p = 0.02) and hypertension (p = 0.04) [40]. Moreover, they had elevated fasting plasma insulin levels (p = 0.02) and lower HDL-C levels (p = 0.02) than men with slow-growing BPH. The annual BPH growth rate correlated positively with diastolic blood pressure (p = 0.01), body mass index (BMI) (p < 0.001), and fasting plasma insulin level (p = 0.008). Conversely, it was negatively correlated with HDL-C level (p = 0.001) [40]. The authors concluded that BPH is a component of metabolic syndrome and that patients with BPH may share the same metabolic abnormalities of a defective insulin-mediated glucose uptake and secondary hyperinsulinemia as patients with metabolic syndrome [40]. These findings support the hypothesis of a causal relationship between high insulin levels and the development of BPH, and they give rise to a hypothesis of increased sympathetic nerve activity in men with BPH. In a recent paper, Ozden et al confirmed that patients affected by BPH and metabolic syndrome had significantly higher median body weight, BMI, serum glucose, serum triglyceride, and prostate-specific antigen (PSA) levels but lower serum HDL-C levels compared with BPH patients without metabolic syndrome. Median annual total prostate growth rate (1.0 ml/yr) and median annual TZ...
growth rate (1.25 ml/yr) were significantly higher in the first group versus the second group (0.64 ml/yr and 0.93 ml/yr, respectively; \( p < 0.05 \)) [41].

Several other studies have suggested a specific association between BPH and diabetes. Specifically, Boon et al showed that men with NIDDM had a higher median annual prostate growth rate as compared with those without diabetes [42]. Moreover, diabetes has been reported to be associated with greater BPH symptom severity [39,42,43]. A possible explanation for the association between BPH and diabetes may result from the fact that these conditions can cause similar urologic symptoms. Both BPH and diabetes are indeed associated with LUTS, including a reduced maximum flow rate and an increased postvoid residual volume. Although the mechanism by which diabetes relates to BPH is unclear, earlier reports have shown that vascular damage induced by type 2 diabetes can promote BPH [38].

Hypertension has also been suggested to be involved in the pathophysiology of BPH. Arterial hypertension occurs in about 25% of patients with BPH [44,45]. Epidemiologic studies have shown that hypertensive men are more likely to develop BPH and to undergo medical and surgical therapy than healthy men [46,47]. These studies have hypothesised that noradrenergic nerves may contribute to the functional component of bladder outlet obstruction due to BPH [46,47]. Animal studies also supported the association between BPH and hypertension [48]. The link between hypertension and BPH suggested by all these studies relies on the activity of the sympathetic nervous system, which has been shown to regulate both arterial tone and voiding physiology [49,50]. It has also been reported that catecholamine levels are high in essential hypertension. Previous studies have hypothesised that the sympathetic nervous system might have an effect on prostate growth by slowing down the apoptotic process [49,51,52].

3.4. Inflammation

In the last few years, the role of chronic inflammation in the pathogenesis of BPH has emerged (Table 1). BPH has indeed been frequently associated with chronic prostatitis. Chronic inflammation is believed to support the process of fibromuscular growth in BPH [53]. Kohnen et al reported inflammatory infiltrate prevalence in 98% of 162 analysed BPH specimens [54]. The Reduction by Dutasteride of Prostate Cancer Events trial also confirmed a significant correlation between BPH-associated inflammation and BPH symptoms [55,56]. The subgroup analysis of the Medical Therapy of Prostate Symptoms Study found a chronic inflammatory infiltrate in 43% of the men. Moreover, inflammation was associated with significantly larger prostates, higher PSA levels, and a greater risk of acute urinary retention [57,58].

The prostate is normally populated by small numbers of T cells, B lymphocytes, macrophages, and mast cells [59,60]. Interestingly, several studies showed that the prostatic tissue in BPH patients contains a disseminated infiltration of T and B lymphocytes and numerous colonies of macrophages [59,61]. The immune response in the prostate is primarily T-cell mediated, with regulatory T cells (CD-4) in the stroma and cytotoxic T cells (CD-8) in the epithelium [62]. In this context, by using analyses of T-cell activation marker expression, Steiner et al demonstrated that such inflammation mediators remain chronically activated [60]. Because local accumulation of activated lymphocytes can cause tissue destruction, high concentrations of cytokines, and consequently tissue rebuilding, might contribute to the pathogenesis of BPH.

Although the factors that trigger the infiltration of those inflammation mediators are partially unidentified, several recent papers have suggested different possible scenarios. Kakehi et al reported that patients with BPH had down-regulation of the gene for macrophage inhibitory cytokine-1, a cytokine with inhibitory effects on macrophage activity [63]. In the context of the intraprostatic location of inflammation elements, the infiltrates predominantly populate the interstitium, collect around epithelial ducts, and dislocate glandular epithelium [64–66]. Bierhoff et al described a "scattered" type of inflammation in BPH characterised by significantly increased diffuse infiltrates of T lymphocytes in fibroblastic and smooth-muscular stromal nodules [61]. Moreover, a decreased infiltration of mesenchymal nodules was recorded relative to the surrounding stroma [59,61].

The inflammation evidenced in BPH may contribute to tissue injury, and cytokines produced by inflammatory cells

<table>
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<th>Study</th>
<th>Evidence</th>
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<tr>
<td>Kohnen et al [54]</td>
<td>High inflammatory infiltrate prevalence in BPH specimens</td>
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<tr>
<td>Kramer et al [53]</td>
<td>Chronic inflammation supporting the process of fibromuscular growth in BPH</td>
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<tr>
<td>Kramer and Marberger [58]</td>
<td>Inflammation associated with significantly larger prostates, higher PSA levels, and greater risk of acute urinary retention</td>
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<tr>
<td>Theyer et al [59]</td>
<td>Inflammation mediators chronically activated in BPH</td>
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<td>Steiner et al [60]</td>
<td>Upregulation of IL-17 in infiltrating T cells</td>
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<td>Steiner et al [68]</td>
<td>Downregulation of the gene for MIC-1 in BPH</td>
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<tr>
<td>Kakehi et al [63]</td>
<td>Upregulation of IL-15 in stromal cells</td>
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<td>Handisurya et al [67]</td>
<td>Upregulation of IFN-γ in basal and stromal cells</td>
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<tr>
<td>Royuela et al [69]</td>
<td>Upregulation of IL-8 in epithelial cells</td>
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<tr>
<td>Giri and Ittmann [70]</td>
<td>Upregulation of IL-8 in epithelial cells</td>
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BPH = benign prostatic hyperplasia; IFN = interferon; IL = interleukin; MIC-1 = macrophage inhibitory cytokine-1; PSA = prostate-specific antigen.
may serve to drive local growth factor production and angiogenesis in the tissues as a “wound healing” response. Indeed, upregulation of a set of proinflammatory cytokines has been reported in BPH tissue, particularly interleukin (IL)-15 in stromal cells [67], IL-17 in infiltrating T cells [68], interferon-γ in basal and stromal cells [69], and IL-8 in epithelial cells [70]. Moreover, IL-8 has also been proposed as the link between chronic prostate inflammation and autocrine/paracrine stromal cell proliferation. It indeed stimulates stromal and epithelial overgrowth by directly promoting the proliferation of senescent epithelial cells and the stromal acquisition of a myofibroblast reactive phenotype and by indirectly inducing FGF-2 secretion [70]. This complex proinflammatory microenvironment is closely related to BPH stromal hyperproliferation. All of the available data seem to suggest that the inflammation-induced damage of the prostatic tissue represents a chronic process of wound healing that activates hyperproliferative processes resulting in the cyclic reactivation of prostatic inflammation.

In the context of inflammation-based tissue remodelling, local hypoxia as a result of increased oxygen demands of proliferating cells also may play a role in the pathophysiology of BPH. Local hypoxia has been shown to induce low levels of reactive oxygen species (ROS) promoting neovascularisation and fibroblast-to-myofibroblast transdifferentiation. Specifically, the secretion of vascular endothelial growth factor (VEGF), FGF-7, TGF-β, FGF-2, and IL-8 is increased under hypoxic in vitro conditions in comparison with normoxia. Levels of TGF-β, VEGF, and IL-8 have been shown to be increased in hypoxic cells. Consistently with those findings based on in vitro studies, immunohistochemistry of hypoxia-inducible factors showed increased activity in BPH tissue. Prostatic stromal cells respond to hypoxia by upregulating the secretion of several growth factors. This suggests that hypoxia can trigger prostatic growth. As a confirmation of the key role of ROS in BPH natural history, upregulation of cyclo-oxygenase has been noted in macrophages and in epithelial cells in hyperplastic tissue [71]. Chronic inflammation has been demonstrated to be a source of oxidative stress that leads to tissue injury in infiltrated areas. This increased oxidative stress has also been monitored in the prostatic and seminal fluid of patients with chronic prostatitis [72,73].

4. Conclusions

Although the pathogenesis of BPH is not yet fully understood, several mechanisms seem to be involved in the development and progression of the disease. These mainly include systemic and local hormonal and vascular alterations as well as prostatic inflammation that would stimulate cellular proliferation. Indeed, recent evidence suggests that BPH is an immune-inflammatory disease. Inflammation would be initiated by an unknown stimulus that would create a proinflammatory environment within the prostate. This theory is confirmed by several autopsy and clinical studies that showed a significant correlation between inflammation and BPH severity and progression. However, further research is required to determine the putative autoantigen, the influence of infiltrating inflammatory cells on the stroma/epithelial cross-talk, and a new classification of BPH quantifying local and systemic inflammatory/immune response in relation to clinical relevance. On the basis of all the available data, the control of inflammation in the clinical management of BPH patients appears to be of fundamental importance. New treatments for BPH investigating these specific inflammatory pathways will be key in the near future.

Conflicts of interest

The authors have nothing to disclose.

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References


Giri D, Ittmann M. Interleukin-8 is a paracrine inducer of fibroblast growth factor 2, a stromal and epithelial growth factor in benign prostatic hyperplasia. Am J Pathol 2001;159:139–47.

