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The Benign Prostatic Hyperplasia and Its Aetiologies

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Abstract
This study aimed at investigating the Benign Prostatic Hyperplasia and Its Aetiologies, therefore th prostatic hyperplasia predominantly involves the stromal compartment of the gland and affects more than 70% of men of 70 years or older with or without obstructive symptoms of benign prostatic hyperplasia. A consensus view is emerging concerning the factors and control systems that modulate cell proliferation and connective tissue biology in the prostate. The purpose of this review is to discuss some of the recent work contributing to the latter in the context of the aetiology of benign prostatic hyperplasia. The current study also reviews the most important findings regarding the key mechanisms involved in the pathophysiology of BPH. The study concluded that 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.

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Introduction

Benign prostatic hyperplasia (BPH), also called prostate gland enlargement (*see figure 1*); is a common condition as men get older. An enlarged prostate gland can cause uncomfortable urinary symptoms, such as blocking the flow of urine out of the bladder. It can also cause bladder, urinary tract or kidney problems (Barry, Fowler, O'leary, Bruskewitz, Holtgrewe, Mebust & Measurement Committee of the American Urological Association, 2017).

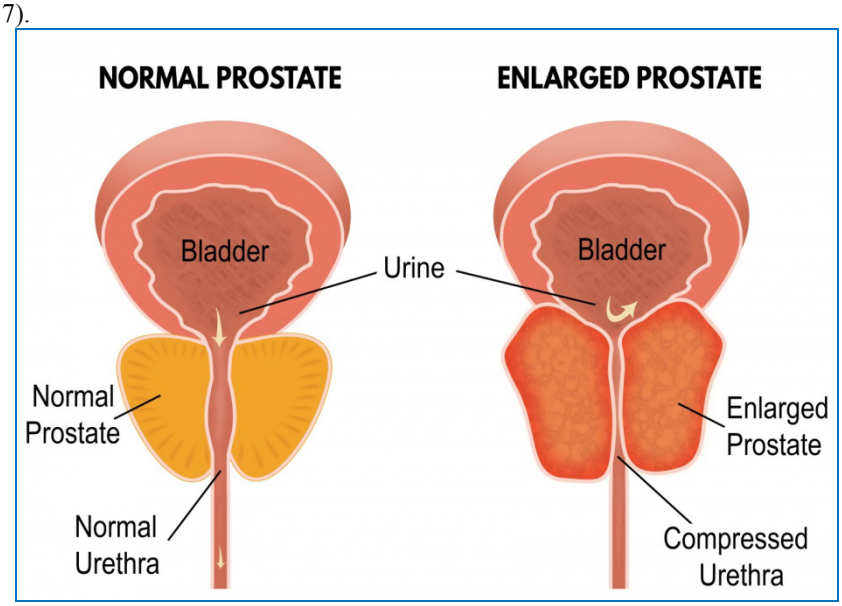

Figure (1): Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate. Chronic bladder outlet obstruction (BOO)

secondary to BPH may lead to urinary retention, renal insufficiency, recurrent urinary tract infections, gross hematuria, and bladder calculi (McVary, Roehrborn, Avins, Barry, Bruskewitz, Donnell & Ulchaker, 2011).

The prostate goes through two main growth periods as a man ages. The first occurs early in puberty, when the prostate doubles in size. The second phase of growth begins around age 25 and continues during most of a man's life. As you age, your prostate may get larger. Benign prostatic hyperplasia often occurs with the second growth phase (Roehrborn, 2005).

As the prostate enlarges, it can then squeeze down on your urethra. The bladder wall becomes thicker. Eventually, the bladder may weaken and lose the ability to empty completely, leaving some urine in the bladder. The narrowing of the urethra and urinary retention--the inability to empty the bladder completely--cause many of the problems associated with benign prostatic hyperplasia. BPH is benign. This means it is not cancer. It does not cause nor lead to cancer. But BPH and cancer can happen at the same time (Kramer, Mitteregger & Marberger, 2007).

Benign prostatic hyperplasia (BPH) is a progressive condition characterized by prostate enlargement accompanied by lower urinary tract symptoms (LUTS) (*see figure 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 (Parsons & Kashefi, 2008).

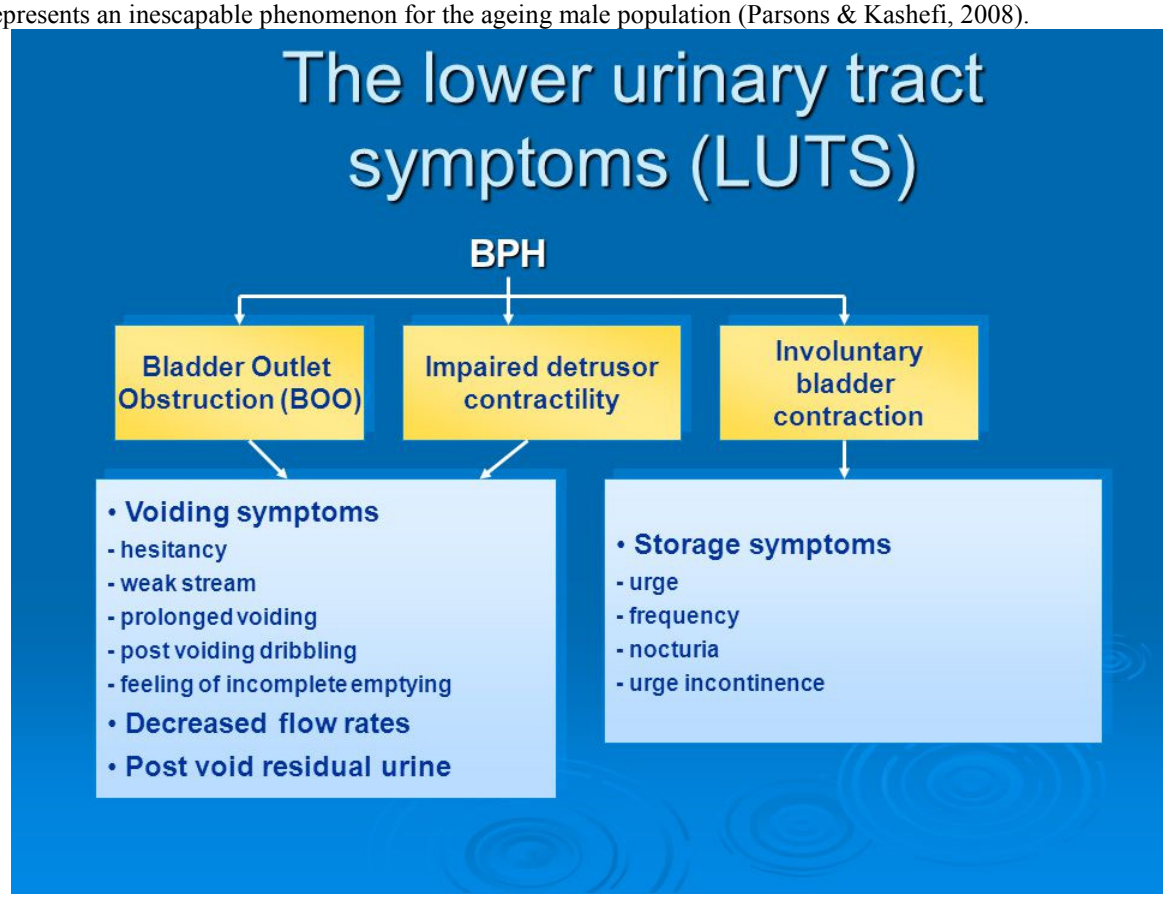

Figure (2): Lower urinary tract symptoms (LUTS)

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 (Irani, Brown, van der Meulen & Emberton, 2003).

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 (Roehrborn, Siami & Barkin, 2009).

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 (Bartoletti, Gavazzi & Cai, 2009).

Problem statement

Prostatic hyperplasia predominantly involves the stromal compartment of the gland and affects more than 70% of men of 70 years or older with or without obstructive symptoms of benign prostatic hyperplasia. A consensus

view is emerging concerning the factors and control systems that modulate cell proliferation and connective tissue biology in the prostate. The purpose of this review is to discuss some of the recent work contributing to the latter in the context of the aetiology of benign prostatic hyperplasia (Eaton, 2003).

The current study also reviews 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. 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.

Tissue remodeling in the ageing prostate

Ageing is the most significant risk factor for the development of BPH and the occurrence of LUTS. Several studies have demonstrated a relationship between age and markers of BPH progression. 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. 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.

In ageing males, a significant tissue-remodeling 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.

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. All of this tissue remodeling leads to alterations of highly specialized 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.

Kiprianou et al (1996) examined the relative expression of two proteins involved in the regulation of prostate apoptosis: transforming growth factor (TGF)–b1 and Bcl-2, a potent apoptosis suppressor.

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. 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-b 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 ant apoptotic 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.

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.

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 5-a 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 relative to normal prostate gland tissue resulting as a permissive, rather than a transformative, mediator in the development of BPH. Moreover, in studies based on the analysis of cadaver specimens, an increased accumulation of DHT was observed in BPH tissues. Conversely, other authors reported no differences in DHT pattern when fresh specimens of prostate tissue were used (Walsh, Hutchins & Ewing, 1983).

Recently, O'Malley et al succeeded in quantifying the expression of four different androgen-responsive genes—ELL associated factor 2 (EAF2, also known as U19), elongation factor, RNA polymerase II, 2 (ELL2), FK506 binding protein 5 (FKBP5), and phosphoserine aminotransferase 1 (PSAT1, also known as PSA)—in either BPH or normal tissue. They demonstrated that all of the assayed genes displayed increased expression in BPH as compared with the adjacent normal glandular tissue. The authors concluded that androgen signalling is significantly elevated in hyperplastic tissue relative to the adjacent normal prostate. Understanding 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.

Metabolic syndrome

The association between metabolic syndrome and BPH has also been studied recently. Hammarsten et al (2001) 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. 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 ($p = 0.04$)]. 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 ($p = 0.001$). 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 hyper-insulinaemia as patients with metabolic syndrome.

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 (2007) 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.

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.

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