

Multifactorial Origins of BPH: Androgens, Inflammation, and Beyond

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ABSTRACT

BPH is a nonmalignant proliferative disorder characterized by progressive enlargement of the prostate gland, involving both stromal and epithelial components. The growth primarily arises from the proliferation of fibroblasts/myofibroblasts and glandular epithelial cells localized in the transition zone surrounding the urethra. Histologically, BPH presents as a multifocal process with heterogeneous tissue composition, featuring varying degrees of stromal nodules and glandular hyperplasia. Understanding this evolving pathophysiology is crucial for guiding treatment and improving patient outcomes.

KEYWORDS: Benign prostatic hyperplasia,, Nonmalignant proliferative disorder, Prostate enlargement, Stromal and epithelial components, Transition zone, Fibroblasts/myofibroblasts

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INTRODUCTION

The human prostate is a walnut sized organ at the base of the urinary bladder considered to be 20 g at 18-20 years of age. The number of men with histological diagnosis of BPH increases at the ages from 51 and 60 years. There are three major causes of morbidity associated with the prostate, benign prostatic hyperplasia (BPH), prostatitis and prostate cancer.

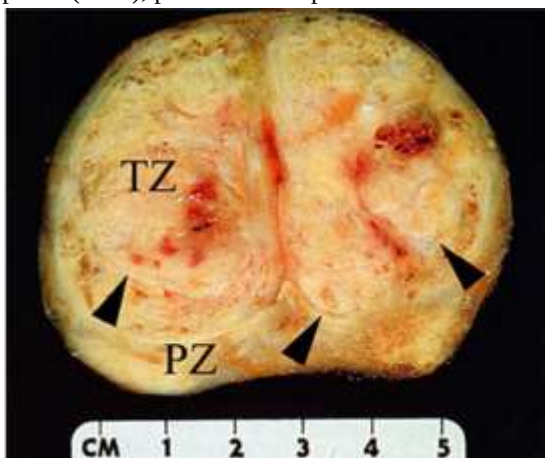


Figure 1. Appearance of BPH in human prostate. Gross anatomy of a human prostate affected by benign prostatic hyperplasia (BPH) in the transitional zone. Hyperplastic nodules (arrowheads) are clearly visible in the transitional zone (TZ) but not the peripheral zone (PZ)

DISCUSSION

BPH has nowadays been reserved for histological diagnosis and the clinical presentation has now been termed benign prostatic enlargement. Although there are many authors that consider BPH as the presence of prostate adenoma(s) causing varying degrees of bladder outlet obstruction (BOO), which may eventually harm the bladder or kidneys. Unlike previous definitions that associated BPH just with lower urinary tract symptoms (LUTS), this definition emphasizes the importance of anatomical and functional obstruction, regardless of symptom presence. The pathogenesis in BPH may consider many hypotheses:

McNeal's Hypothesis (Reawakening hypothesis): BPH results from reactivated inductive signaling in adult prostatic stroma, leading to focal nodule formation in the transition zone. These nodules may be purely stromal or epithelial-invaded, forming new glandular structures. Human BPH glands appear histologically normal; the abnormality lies in their focal organization.

Androgen Dependence: Levels of serum testosterone decrease during the past few years against a constant level of estradiol giving the result of the change in the androgen/estrogen ratio which has been hypothesized that it is enough to promote the growth of BPH. While aging is crucial for benign prostatic

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hyperplasia (BPH) development, androgens also play a key but debated role. Testosterone and its more potent metabolite, dihydrotestosterone (DHT), act via the androgen receptor (AR), which is highly expressed in prostate luminal cells. DHT, produced by 5 α -reductase type 2, binds AR with greater affinity than testosterone, driving prostate growth. Evidence includes males with 5 α -reductase deficiency, who exhibit underdeveloped prostates lacking epithelial tissue. Paradoxically, androgen therapy in hypogonadal men does not raise BPH risk, suggesting prostate sensitivity depends on local DHT levels rather than systemic androgens. Tissue DHT remains stable with aging, keeping AR saturated and sustaining BPH growth. Clinically, 5 α -reductase inhibitors reduce prostate volume and improve urinary symptoms, but effects take approximately 6 months, implying other factors drive BPH progression. Thus, while androgens are essential for normal prostate function, their exact role in BPH pathogenesis remains unclear, highlighting the complexity of this condition.

Estrogens: Even though they act in opposition to androgens, new evidence shows that they may play a significant role in BPH development, potentially working synergistically with androgens. In aging men, the estrogen:androgen ratio increases due to declining testosterone levels while estrogen remains stable, potentially contributing to BPH pathogenesis. Metabolic dysfunction exacerbates this hormonal imbalance through increased aromatase activity in adipose tissue, converting androgens to estrogens. In animals, estrogen administration can induce prostatic hyperplasia, mediated through estrogen receptors ER α (stromal-localized) and ER β (epithelial-localized). While ER α promotes stromal proliferation and paracrine epithelial effects, ER β appears to have pro-apoptotic properties. This paradox may be resolved by tissue-specific receptor dominance, as stromal cells contain higher aromatase levels, favoring ER α -mediated growth effects.

Obesity / Chronic inflammation: its well known that obesity is a pro inflammatory condition, and there is evidence that show that chronic inflammation links to BPH severity, progression and complications. NF- κ B signaling activation and expression of androgen receptor variant 7 (AR-V7) correlate with BPH progression and increased prostate volume, indicating a molecular link between inflammation and hyperplastic growth. Also stromal nodules in BPH contain elevated levels of T and B lymphocytes, confirming an active immune response. Interstitial and periglandular inflammation is common in human BPH, with increased pro-inflammatory cytokines (IL-2, IL-8, IL-17, IFN γ). These cytokines have direct mitogenic effects on prostate tissue, particularly in early BPH development.

Genetics: There's an hereditary influence for BPH, its 3.3 increased the relative risk comparing monozygotic versus

dizygotic twins. The risk factors include from losses in the Y chromosome to single nucleotide polymorphism. Suggesting potential sex chromosome involvement in disease pathogenesis. Polymorphisms in the 5 α -reductase type II gene (SRD5A2) correlate with BPH incidence, supporting the hormonal basis of the condition

CONCLUSION

BPH is a multifactorial condition involving nonmalignant proliferation of prostate stromal and epithelial cells, primarily in the transitional zone. Hormonal influences: Androgens are permissive for BPH development, but estrogen/testosterone ratio changes with aging may play a role. Chronic prostatic inflammation is common and linked to larger prostate volumes, symptom progression, and urinary retention. Also, there is an hereditary factor that contributes to the BPH risk that has been studied for many years.

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