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REVIEW

The Etiology and Pathogenesis of Benign Prostatic Hyperplasia: The Roles of Sex Hormones and Anatomy

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Abstract: Benign prostatic hyperplasia (BPH) mainly causes lower urinary tract symptoms in ageing men, but its exact etiology and pathogenesis have not been established. The objective of this review was to design an update on the advances of human BPH research. We undertook a literature search for identifying studies of the roles of sex hormones (androgens and estrogens) in the onset and development of human BPH using the Pubmed database. In literature, many studies have indicated that ageing and obesity are the factors for preceding the onset of BPH. No evidence for the role of testosterone (T) or dihydrotestosterone (DHT) is found in BPH initiation. Since BPH exclusively occurs in the transitional zone (TZ) surrounding the urethra, it is postulated that years of exposure to uncharacterized urinary toxins could disrupt the homeostasis of the stroma and/or epithelium of this prostatic zone that are typically occurring in ageing men. After cellular damage and subsequent inflammation generated, the intraprostatic DHT produced mainly from T by 5α-reductase promotes BPH development. Further, estrogens could take part in the nodular proliferation of stromal cells in some BPH patients. The confounding of BPH may attenuate the development of prostate tumor in the TZ. In conclusion, evidence in literature suggests that androgens are not etiological factors for BPH, and intraprostatic DHT along with chronic inflammation are mainly responsible for nodular proliferation of stromal and/or epithelial cells in prostatic TZ. The urinary factors for the etiology of BPH and BPH as a prediction of PCa progression still need further investigation.

Keywords: benign prostatic hyperplasia, tissue homeostasis, etiology, nodular proliferation, stroma, epithelium, androgens, steroid sex hormones

Introduction

Benign prostatic hyperplasia (BPH) describes nonmalignant growth or hyperplasia of the prostate gland that is often found in men over40 years old, and its prevalence increases with advancing age, 50–60% in men in their 60s and 80–90% in those older than 70 years old,[1,2] and this prostate disease is almost three times more than the prostate cancer (PCa) cases in these ageing men.[3] A recent systematic analysis of BPH from 2000–2019 in 204 countries and territories around the world indicates that there are 94 million prevalent cases of BPH in 2019 globally as compared to 51.1 million cases in 2000, which is increased by 70.5% during the past 20 years.[4] Because of compression of the prostatic urethra, BPH can cause clinical manifestations of lower urinary tract symptoms (LUTS), urinary retention (acute and chronic), and bladder damage,[5–7] and there is a great need for a better understanding of the pathophysiology of BPH initiation and progression, a prerequisite for development of novel medical treatment options as well as prevention strategies for more effective management of this disease.

The structure of the human prostate can be divided into three different zones: the central zone (CZ), peripheral zone (PZ), and transitional zone (TZ).[8–10] The CZ is a cone-shaped region of the prostate that surrounds the ejaculatory ducts, whereas the PZ covers most of the CZ, and some extends and partially surrounds the distal portion of the urethra, and the

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TZ is the smaller part, approximately 5% of the normal prostate mass, that surrounds the urethra between the bladder and the verumontanum (the area where the ejactulatory ducts feed into the urethra).[8,10] Importantly, it has been documented that prostatitis and prostatic tumors are mainly found in the PZ. BPH in the TZ, in which expansion of hyperplastic nodules results in compression or narrowing of the urethra and the partial bladder outlet obstruction or LUTS,[8,10,11] suggests that LUTS due to BPH is more precisely caused by the expansion of the TZ rather than the prostate size. Indeed, the prostate size can predict certain aspects of the natural history of LUTS and BPH,[5] but there is no association between the prostate size and incident LUTS in men treated with dutasteride.[12] Therefore, more quantitative imaging of the TZ or the prostatic urethra may be required in the evaluation of LUTS and urinary retention, especially in BPH patients under treatment.

The histological structure of the human prostatic gland mainly consists of glandular epithelium and fibromuscular stroma. The epithelium contains at least three types of cells (columnar luminal epithelial cells, basal cells, and neuroendocrine cells), whereas the stroma is made up of abundant smooth muscle cells, fibroblasts, blood vessels, and nerves.[10,13] Both histological and molecular profiling studies have shown that the hyperplastic nodules of BPH in the TZ are characterized by nodular proliferation of variable components of the epithelium including basal cells and the stroma, ranging from predominantly epithelial to pure stromal nodules – a condition of the nonmalignant growth of prostate tissue that occurs with leukocyte infiltration with production of proinflammatory cytokines, epithelial and stromal atrophy, and the production of growth factors (ie, TGF-β, bFGF, and neuroendocrine peptides).[10,14–16] Decades of epidemiological studies have established two risk factors for the development of BPH in men: ageing (over 40 years old) and functioning testicles at the time of puberty.[16] However, the underlying mechanisms involved in the association of ageing and the (dys)function of the distant testicles with BPH, presented by the abnormal growth of smooth muscle tissue or stroma and glandular epithelial tissue, in the prostate are far from clear. The objective of this review was to summarize recent studies of endocrine background for the development of BPH.

The Etiology of BPH

The etiological factors are defined as necessary conditions for preceding the onset of a disease. Fully understanding the etiological factor(s) of BPH is a prerequisite for developing effective prevention strategies for this prostate disorder. First, as mentioned above, BPH is an ageing-dependent prostatic disorder,[1,2] implying that the etiologic factor(s) for initiation of BPH must be age-related. Second, histologically BPH is presented by the nodular proliferation of epithelial and/or stromal cells in the TZ,[8,10,11] indicating that these factor(s) are the cellular signaling or component that is restrictedly activated in the TZ. Third, because the hyperplastic nodules of BPH are localized predominantly in different compartments (stroma and/or epithelium) of the TZ between different patients,[10,14–16] it is possible that the initiation factor(s) may be different in the different tissue compartments, but they have the same function by which the cell proliferation can be stimulated by growth factors such as testosterone (T) and dihydrotestosterone (DHT).

There have been three different theories that have been proposed based on earlier studies for the possible causes of BPH: (1) the accumulation of DHT, a product of T by catalytic activity of 5α-reductase (DHT hypothesis), (2) reawakening of the embryonic induction potential of prostatic stroma and/or epithelium by the stromal-epithelial interactions as seen in the development of human fetal prostate (embryonic reawakening hypothesis), and (3) an increase in stem cells or clonal expansion of stem cells (stem cell hypothesis).[17–19] To our knowledge, there is still a lack of convincing, direct evidence in literature supporting any of these theories for explaining the nature of BPH occurrence in the prostate of ageing men, specifically in the TZ as described above.

T and its metabolite DHT are two main active forms of androgens in the human body,[20] and both are required for the growth of fetal prostate in numerous experimental studies[21–23] as well as for the development of the prostate.[24] Therefore, the roles of T and/or DHT have become a focus in the investigation of BPH initiation. However, the contribution of these androgens to the initiation of BPH can be questionable based on the following studies of adults who were not diagnosed with BPH yet:

(1) Large-scale cohort studies of healthy men aged over 40 years old have shown either no correlation[25–27] or a negative correlation of serum T with prostate size including the size of the TZ and prostate growth over a 4-year period.[28,29] Furthermore, serum DHT is also not correlated with prostate size in this healthy population.[29] These data suggest that serum androgens may not predispose men to the BPH initiation.

(2) Medical castration of healthy men (35–55 years old) using acyline, a long-acting GnRH-antagonist reduces 70% of prostatic T and 80% of DHT that have no effect on prostate cell proliferation, apoptosis, and androgen-regulated protein expression,[30] suggesting that the physiological levels of intraprostatic T and DHT may not be required for prostate cell proliferation in healthy prostates or probably prior to the onset of BPH.

(3) DHT treatment of healthy men (over 50 years old) increases serum DHT but does not affect the prostate volume,[31] and similar results are seen in T treatment of young men (21–39 years old), showing that, despite a significant elevation of serum T, no growth of the prostate in response to T treatment has been demonstrated.[32]

(4) BPH and hypogonadism are two common disorders in ageing men, and T replacement therapy (TRT) has often been used for treatment of hypogonadism including late-onset hypogonadism in patients without BPH or LUTS.[33–35] The increasing risk for initiation of BPH or prostate tumor related to TRT has been concerned in these patients. Although TRT significantly elevates the serum T and improves all aspects of sex function,[33,34] it does not increase the prostate size or cause LUTS that specifically relates to TRT in these T-treated ageing men.[36–41] A histological study confirms that 1-year TRT has no effect on cell death and proliferation or atrophy of prostate tissue.[36]

Taking all these findings together, we may conclude that T or DHT does not seem to be enough to initiate BPH in adult men, even though they are effective in the stimulation of normal prostate growth from fetal to puberty as well as in the maintenance of prostatic homeostasis afterward.[42] We have also noticed that age-related metabolic aberrations, especially obesity, may be a risk factor for the initiation or development of BPH.[43–45] It has been estimated that a 1 kg/m^2 increase in body mass index (BMI) is correlated with a 0.4 mL increase in prostate volume, and BMI > 35 kg/m^2 (obese) has a 3.5-fold increased risk of prostate enlargement compared to non-obese BMI < 25 kg/m^2.[46] The potentially underlying links of the obesity to BPH are unknown.

Thus far, there has been a lack of investigating the role of anatomical location of BPH, the TZ of the prostate, in the initiation of this age-dependent prostate disorder. The TZ surrounds the urethra that conducts urine from the bladder to the exterior. This function distinguishes the TZ from the other prostate tissues (ie, the CZ and PZ). Therefore, we hypothesize that the etiologic factors for BPH may come from years of exposure to urinary toxins or waste substances including xenobiotics and toxic metabolites that are typically occurring in ageing persons[47,48] as well as possible pathogens such as from urinary tract infection specifically occurring in the urethra. These factors under the condition of poor tissue repair in ageing men could cause significant cellular damage of the stroma and/or epithelium in the TZ, which subsequently generate a feedback response such as leukocyte infiltration, production of both proinflammatory and anti-inflammatory factors by activated leukocytes, and stimulation of aberrant cellular proliferation (Figure 1).

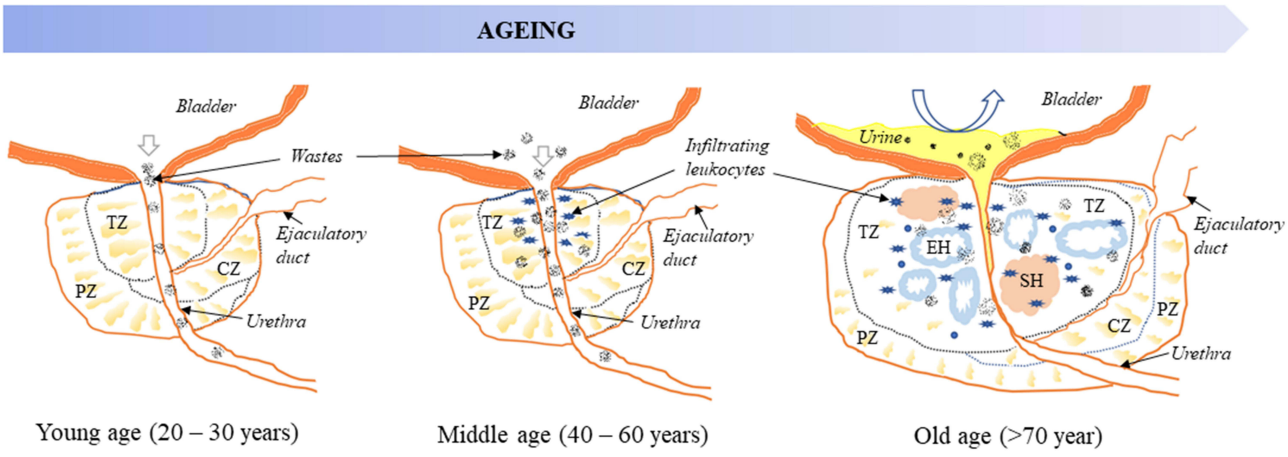

Figure 1 The phase diagram of BPH development (etiology and pathogenesis) with age. At a young age, the functional organization of prostatic tissues including transitional zone (TZ), central zone (CZ), peripheral zone (PZ), urethra, and ejaculatory duct is well maintained by tissue homeostasis. At a middle age, after years of exposure to the waste chemicals from the urine, the tissue homeostasis of TZ is disrupted by accumulation of urinary wastes within the TZ and leukocyte infiltration (the onset of BPH) (hypothesis). From the middle to old age, after irreversible disruption of tissue homeostasis, inflammatory mediators induce cell death and fibrosis, while locally synthesized DHT and growth factors stimulate cell proliferation – to form epithelial hyperplasia (EH) and stromal hyperplasia (SH), which may represent different subtypes of TZ enlargement and lead to urethra obstruction.

The Pathogenesis of BPH

The pathogenesis is defined as the process and factors associated with the perpetuation or progression of a disease. It has been known that both prostate volume (≥ 30 g) and age (≥ 62 years old) are two baseline predictors for an increase in risk of BPH progression,[49] and a histological hallmark of BPH progression is enlargement of the prostate that is caused by nodular proliferation of epithelial and/or stromal cells in the TZ. The requirement of intact testicles for BPH progression was initially from early surgical castration for treatment of prostate enlargement of BPH patients, which reported that there were 51.5–84% of patients showing a decrease in prostate size after castration,[50] which is confirmed by 31.4% (range = 19–55%) prostate volume loss in BPH patients after 2–3 months of castration.[51] Furthermore, a small group of patients at the age of 57–80 years old with no testicular function before puberty (panhypopituitarism) or throughout life (hypogonadotropic hypogonadism or prepubertal castration) have atrophic prostates histologically, whereas those who have functioning testicles develop BPH.[52] However, the exact mechanisms by which the testicular function mediates the progression of BPH remain unclear.

T is almost exclusively synthesized from cholesterol in mature Leydig cells of the testicles (termed as testicular T), and it is released to the bloodstream and subsequently reaches its target organs such as the prostate.[53,54] In addition to the testicles, some extragonadal biosynthesis of T from dehydroepiandrosterone within specific tissues has been described (termed as adrenal T),[55] but the contribution of adrenal T to the physiological effects on men including prostate growth is minor.[52,56] To answer if testicular T is part of testicle function mediating BPH progression, the effect of serum T levels on prostate enlargement in BPH patients has been extensively investigated. First, the correlation of serum T levels with diseased prostate size in BPH patients has been analyzed in many population-based cohort studies. As compared with healthy men, patients with BPH have significantly lower serum T levels,[57] but different results have been found in different cross-sectional studies in BPH patients, indicated by either a positive correlation[58,59] or no such correlation.[25,60–62] These inconsistent results may be due to BPH heterogeneity or limited sample size in each study. Second, BPH can be developed in some hypogonadism patients with testicle failure or low serum T levels (< 3 ng/mL),[62] particularly in ageing men with Klinefelter syndrome and one with undetectable T in the plasma.[63,64] Third, numerous retrospective or clinical trials have demonstrated that TRT increases serum T to normal levels in BPH patients who are endogenous T deficiency (hypogonadism), but it either has no further influence on prostate size or reduces the severity of LUTS.[37,38,65,66] Taken together, these studies at least imply that a high level of serum T may be not required for BPH progression, and, in some cases, T may not be needed at all for the pathogenesis of BPH.

Both T and DHT bind to the same receptor – androgen receptor (AR) – for their biological activities, and DHT can be produced by reduction of T via one of three types of 5α-reductase isozymes that have been identified at different tissues of adult human body, indicated by a predominant expression of SRD5α-1 in the skin and liver, SRD5α-2 in the prostate, and SRD5α-3 in the skin, brain and mammary gland.[67,68] A significant role of DHT in BPH could be found as indicated by the facts that the binding affinity of DHT to AR is roughly four times higher than that of T,[69] and in elderly men with BPH, the majority of DHT may be produced by the prostate[70] that is confirmed by the fact that the levels of intraprostatic DHT are 6–10-fold higher than serum DHT.[71] The intraprostatic DHT can be pooled from: (1) reduction of T, in situ, by intraprostatic SRD5α, (2) synthesis directly from 17-hydroxypregnenolone and 17-hydroxyprogesterone, and (3) intracrine reverse synthesis from the DHT metabolite androstanediol (3α-diol) through the oxidative function of 3α-hydroxysteroid dehydrogenase.[71] So that, despite a decrease in serum T with ageing,[2] the serum or intraprostatic DHT level can remain at normal adult levels in elderly men. Indeed, serum DHT levels either remain constant throughout the time of BPH development or are positively correlated with prostate size.[61,72] Other studies have also demonstrated a positive correlation of intraprostatic DHT with prostate size[73] as well as with protein synthesis of both stromal and epithelial cells,[74] which may suggest a dominant role of intraprostatic DHT in the promotion of protein synthesis and proliferation in both prostatic epithelial and stromal cells. The central role of DHT in the development of BPH has been further verified by successful clinical use of finasteride (an inhibitor of SRD5α-2, 3) or dutasteride (an inhibitor of SRD5α-1, 2, 3) in the management of BPH,[68,75–77] showing that dutasteride at a dosage of 0.5 mg/day or finasteride at 5 mg/day significantly reduces serum or intraprostatic DHT of over 70% and prostate volume of approximately 30%.[75,76]

Androgens (ie, DHT) may activate two distinct molecular signaling cascades for their actions in the stimulation of prostate tumor growth.[78,79] The first pathway is the DNA binding-dependent (DBD) pathway, in which androgen binds to

AR to form a complex that translocates to the nucleus as a gene transcription factor where it modulates the transcription of androgen response elements containing target genes. It has been reported that AR regulates transcription of 1.5–4.3% of all gene transcripts within LNCaP cells, a representative cell line of androgen-responsive PCa,[80] but it varies in different cell types.[81] The second pathway is te non-DNA binding-dependent (non-DBD) pathways that include the non-genomic pathway (activated by androgens), outlaw pathway (activated by IL-6, IL-8, PTEN mutation), and bypass pathway (neither androgens nor AR).[79] However, whether DHT in the pathogenesis of BPH activates the same pathways as it does in the stimulation of prostate tumor growth has barely been reported in the literature. It would be postulated that the intraprostatic DHT in BPH may activate both the DBD and non-genomic pathways in addition to the outlaw pathway (ie, YAP1) activated by both inflammatory cytokines (ie, IL-6, IL-8) and growth factors (ie, TGF-β, bFGF) produced by infiltrating leukocytes.[14–16,82,83] A complete understanding of DHT-mediating molecular pathways by which BPH is developed is required for development of any new therapeutic approaches to treat BPH.

Besides androgens, the testicles of elderly men produce approximately 20% of circulating estrogens (E2), and the remainder comes from conversion of T by aromatase in tissues (ie, adipose, brain, skin, and bone).[84] Many epidemiological studies have reported a positive correlation of serum E2 with BPH volume,[58,59,62,85–88] and serum E2 levels are an independent predictor of BPH.[89] Further, intraprostatic levels of estradiol and estrone are higher than those of androgens in BPH patients.[90] However, immunohistochemical studies have shown that estrogen receptor (ER)-α is predominantly expressed in the stroma and mediates cell proliferation,[91] and its expression is positively correlated with prostate size in BPH patients,[87] whereas ER-β mainly expresses in the epithelium but its activation induces apoptosis and suppresses prostate growth,[92,93] suggesting that E2 may have different impacts on BPH progression – promotion of nodular proliferation in stroma but not in epithelium of the TZ. To date, clinical trials with aromatase inhibitors have not yielded dramatic positive results in the treatment of BPH.[94]

In addition to the steroid hormones, several in vitro studies have demonstrated the promoting effect of spermatocele derived testicular epididymal plasma on the growth of human prostate cells and suggest the presence of at least two separate growth-promoting factors, one for stromal cells and one for epithelial cells,[95–97] which may include pigment epithelium-derived factor (PEDF) that stimulates benign prostatic hyperplasia stroma in vitro.[98] Thus, the concept that testicular epididymal secretory proteins as part of testicle function are required for abnormal prostate growth in BPH warrants continued consideration.

The Confounding of BPH and Prostate Tumor by Age

Similar to BPH, PCa is also an age-dependent prostate disorder, indicated by the fact that 23% of men in their 50s, 34.7% in their 60s, and 45.5% of those aged older than 70 years have incidental, preclinical PCa,[99,100] indicating that both nonmalignant (benign, BPH) and malignant (tumor cells, PCa) cells may be proliferating within the same prostate gland of some aging men, especially those aged over 70 years old. Indeed, transurethral resection of prostate (TURP) is a surgical pathology practice for clinically diagnosed BPH, and prostate tumors are incidentally found in a significant number (up to 28.7%) of TURP specimens.[101–103] Both are hormone-dependent growth and response to antiandrogen therapy, and risk factors such as prostate inflammation and metabolic disruption have key roles in the development of both diseases.[104] Despite these commonalities, BPH and prostate tumors are localized differently in the prostate. As mention above (Figure 1), BPH is exclusively developed in the TZ, whereas prostate tumors have been found in all three zones, but mainly in the PZ (~ 70%) and less frequently in the TZ (up to 25%).[105–109] As compared with PZ tumors, TZ tumors have a larger volume with lower pathological stage or Gleason scores and better clinical outcomes,[108–111] suggesting that the confounding of BPH could be used for an accurate prediction of PCa progression. However, whether this confounding reflects a causal relation with TZ tumor and shared risk factors or pathophysiological mechanisms requires further investigation. Recently, magnetic resonance imaging has been successfully used for quantitative measurement of BPH and TZ tumors.[112–115] Thus, further studies using improved imaging technology are required to establish BPH as a suppressive factor for PCa development, especially TZ tumors, which could improve the accuracy of prognostication and expedite intervention by consideration of BPH, potentially reducing PCa-caused mortality.

Conclusion

BPH is characterized as progressive enlargement of the prostate and is common in adult men. Without treatment, it may cause severe voiding and storage symptoms in the bladder that can be progressed to acute urinary retention requiring Foley catheter placement. Hence, the strategic priorities for improving prostate health as men age are to reduce the risk of BPH, or to delay its progression after diagnosis. The pathophysiology of BPH has been extensively studied over many years, but the exact etiology and pathogenesis of this common prostate disorder are still not fully understood. Evidence from limited literature as reviewed here suggests that androgens are not etiological factors for the initiation of BPH. Based on the location inside the prostate (the TZ) that BPH affects, we hypothesize that years of exposure to the urinary toxins that specially appear in ageing and obese men lead to a disruption of tissue homeostasis in the TZ – the onset of BPH. As is the case of BPH progression, it is clear that the nodular hyperplasia in either stroma or epithelium or both is promoted by a cascade of cellular responses to the molecular events of intraprostatic DHT, chronic inflammation, E2, and perhaps other growth factors (eg, PEDF) from the testicles (Figure 1). The potential of confounding of BPH for an accurate prediction of PCa progression is briefly reviewed. Further directions in the field of BPH research should include: (1) investigating the difference of urine composition between healthy and BPH populations and the pathological factors (if any) that regulate the proliferation of prostatic stromal and epithelial cells in BPH patients who may have different pathological subtypes, as suggested by a recent study,[15] respectively, (2) the confounding of BPH as an accurate prediction of PCa progression warrants further investigation.

Abbreviations

bFGF, basic fibroblast growth factor; BMI, body mass index; BPH, benign prostatic hyperplasia; CZ, central zone; DBD, DNA-binding dependent; DHT, dihydrotestosterone; E2, estrogens; ER, estrogen receptor; GnRH, gonadotropin-releasing hormone; LUTS, lower urinary tract symptoms; IL, interleukin; PEDF, pigment epithelium-derived factor; PZ, peripheral zone; SRD, steroid reductase; T, testosterone; TGF, transforming growth factor; TRT, T replacement therapy; TURP, transurethral resection of prostate; TZ, transitional zone.

Ethics Approval and Consent to Participate

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Disclosure

All authors have no competing interest to declare.

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