# **Review Article**

# **Review on Benign prostatic hyperplasia (BPH)**

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#### ABSTRACT

At birth, man prostate is about the size of a pea and undergoes changes during the course of man's life. It grows slightly until puberty and then it begins to enlarge gradually, attaining normal adult size and shape excessive cell proliferation can increase prostate weight and size, leads to constrict the urethra, inducing various symptoms including nocturia, weak urinary stream, dysuria and bladder outlet obstruction incomplete bladder emptying. Surgery is the ultimate solution, but pharmacotherapy is often tried first and continued for as long as feasible. Allopathic medicines used in the treatment of BPH are associated with a number of side effects and post-surgical complications are more with the surgical procedures like Prostatectomy, in this review all aspects of BPH were discussed.

Key words: BPH, Hyperplasia, Testosterone.

#### **INTRODUCTION**

Benign prostatic hyperplasia is often used to mean either an enlarged prostate or urinary obstruction [1]. It is common to be normal with advancing age in up to 90% of men by age 80. BPH may defined as a life altering condition requiring urgent medical innervations in a serious medical disorder associated with major complication[1].

It is common condition in elderly men with an estimated prevalence of up 80% [2]. At the age of fifty the prostate begins to increase gradually causing dysuria. In the normal prostate texture there is 55 % of soft muscle fibers, 45 % of connective tissues and epithelium. In case of BPH, epithelium as well as connective tissue thrive and hyperplased of cells and prostate soft muscle. While hyperplased prostate presses urethra to contracts, and stream of urination weakens the muscle of urinary bladder hypertrophies and loses tonicity. It is considered that BPH develops when the balance of androgen and estrogens discomfits. A male hormone testosterone in prostate exposed to enzyme 5 -reductase is turned into active dihydrotestosterone and exposed to enzyme aromatase is turned into estrogen. The progression of Disease is thought to be dependent on growth factors, adrenergic stimulation, inflammatory processes and testosterone to dihydrotestosterone insulin- like growth factors [3]. leads to enlarge gradually, attaining normal adult size and shape excessive cell proliferation can increase prostate weight and size, leads to constrict the urethra, inducing various symptoms including nocturia, weak urinary stream, dysuria and bladder outlet obstruction incomplete bladder emptying. Here an attempt was made to discuss all aspects of BPH.

# 2. Anatomy and physiology of prostate

The prostate is a major sex gland of the male [4]. The prostate is a walnut sized gland that forms a part of male reproductive system. It is located in front of rectum and just below the

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urinary bladder, where urine is stored. The prostate also surrounds urethra, the canal through urine passes out of body [5].



(http://medicineworld.org/cancer/prostate/prostate-cancer-blog.html) Fig.1: Anatomy of prostate.

It secretes seminal fluids which contributes about 15 percent of ejaculate volume. The gland consists of distinct anatomical zones which have different disease susceptibility. The peripheral zone is site of development of prostate cancer. The transition zone, which separates the peripheral zone from the central zone, is site of hyperplasia (i.e. increased cell number) [6]. The prostate, the prostatic urethra and the bladder neck play critical role in the normal delivery of sperm in sexual act. However the major clinical interest in the growth and function of prostate has resulted from the occurrence of malignant neoplasms and infection. Although physiological parallels may abundant, anatomic parallels are few, in dogs as in man the prostate is intimately associated with bladder neck, where in the opossum many prostatic glands are disseminated along the urethra The Principal function of prostate gland is fertility (Contributing most of the volume of ejaculate). prostatic secretion is rich in fructose, providing a substrate for oxidative metabolism of spermatozoa and also prostate specific antigens, a serine protease in humans kallikrein family which is thought to liquefy the viscous seminal fluid facilitating motility of spermatozoa [7].

#### **3.** Hormones and the Prostate

Prostate enlargement is strongly related to normal aging BPH can be called as an aspect of male menopause because an increased ratio of estrogen to testosterone is active in BPH conversely, in women passing through menopause the ratio of testosterone to estrogen increases. It is generally accepted that hormone ratios and hormone clearance are involved in BPH, but the exact way in which these lead to the enlargement has yet to be definitively explained. As can be seen in Figure 2, testosterone secretion is highly regulated by way of feedback loops involving the pituitary gland and the hypothalamus. In as much as renewed prostate growth appears in later life at the point at which actual testosterone production is in significant decline, it is plausible to suspect that secretory signals may play a role in altering the clearance of testosterone from the tissues affected.

There is increase in testosterone level in male during adolescence. At the age of 50 and thereafter testosterone level decreases. Decrease in testosterone leads to compensatory release of other hormones which then stimulate testosterone production, leads to increase in transformation of testosterone into dihydrotestosterone (DHT) or decrease in clearance of DHT from prostate. Enzyme 5 -reductase enzyme is responsible for conversion of testosterone into DHT. This DHT cause the enlargement of the prostate. DHT binds to androgen receptors specific receptors on the prostate cells. It then is transported into the

nucleus of these cells where it attaches to the DNA and ultimately turns to prostate growth [10]



Figure2: Glandular Regulation of Androgen Secretion

The above is an illustration of the hypothalamic - pituitary - gonadal axis with site action (X) of gonadotropin-releasing hormone (GnRH) agonists and the sites of the inhibitory (-) and stimulatory (+) actions of testosterone (T)

Another hormone which plays a significant role in the development of BPH is prolactin. Prolactin both increases the conversion of testosterone to DHT and the binding of androgens to prostate cells. Prolactin production itself is increased by stress, alcohol and aging. One counterweight to prolactin is the hormone melatonin, much in the news as an "anti-aging" hormone. Significantly, melatonin, which acts to check prolactin production, declines even as prolactin levels increase with age. This is not to suggest that melatonin supplementation is an answer to BPH, but rather to indicate that various factors related to estrogen binding to receptors in the prostate increase in later life must be considered.

It should be kept in mind that many of the factors found in the various forms of prostatitis may come into play in BPH. Inflammation is a common and significant element in BPH. Also of importance are spasms in the smooth muscles which line the urethra and the neck of the bladder, the inability to relax the sphincters constructed of these smooth muscles, a weakened ability to contract the bladder upon command, and so forth and so on. None of these factors are readily influenced by drug approaches to BPH which are intended specifically to inhibit the conversion of testosterone to DHT [8-9].

# **CRITICAL REVIEW IN PHARMACEUTICAL SCIENCES**

## 4. Role of testosterone in BPH

Testosterone is principal circulating androgen. In man, it is secreted primarily by testes, with the renal glands providing a minor contribution. To be maximally active in the prostate, testosterone converted to dihydrotestosterone (DHT) by the enzyme 5 alpha-reductase (fig3)

Studies in rats have demonstrated that, at equivalent androgen concentration in the prostate. DHT is about twice as potent as testosterone. Also has greater affinity for the androgen receptors than testosterone, permitting to accumulate in the prostate when circulating testosterone level is low.

This dual action of alpha-reductase in the androgen physiology explains the critical importance of these enzymes in stimulation of prostate growth [9].



Fig 3: Pathways to Prostatic Hyperplasia and Urinary Urgency

# 5. Factors causing benign prostatic hyperplasia

**5.1 Age** is associated with increased prostate size related to BPH. Hyperplasia is initially seen in about fifth decade, and increase with age. About 40% of men aged > 50 years and 90% of men aged > 80 years have microscopic histopathological evidence of BPH.

**5.2 Genetic:** In studies of inherited factors predisposing to the development of BPH, candidate's genetic polymorphisms are the androgen receptors and the SRS5A2 gene coding for the 5- alpha reductase enzymes responsible for the conversion of testosterone to dihydrotestosterone (DHT) which is about five times more potent at the androgen receptors. DHT appears to be necessary for the development of BPH.

# **5.3 Dietary Factors**

Some small studies have suggested the following:

- Coffee has been associated with a higher risk for BPH. There is some indication that drinking green tea, however, may benefit the prostate.
- Moderate alcohol consumption may be protective. (Heavy alcohol consumption, however, may increase the risk for lower urinary tract symptoms, and, in any case, is harmful.)
- Genistein, a chemical found in soy, reduced the growth of BPH tissue in the laboratory. Although Asians have a low incidence of BPH and prostate cancer and also have diets

rich in soy, it is not yet known if eating soy products will reduce the risk of BPH or improve any symptoms.

- One recent well published study found an association between a lower risk for BPH and high intake of fruits and a higher risk for BPH with a high intake of butter and margarine.
- Zinc is of interest because it accumulates to the highest levels in a body in either a normal prostate or one enlarged from benign prostate hyperplasia. Some laboratory studies suggest that zinc might inhibit activation of prostate cancer cells. A 2003 study, however, reported that men taking zinc supplements in high doses (100 mg) had a higher risk for advanced prostate cancer. Of note, such men also took higher levels of calcium, iron, and other supplements that might have biased these results. More research is needed to determine the role of zinc on prostate health [11]

# **5.4 Hormonal Changes**

- Male Hormone: Androgens most likely play a role in prostate growth. The most important androgen is testosterone, which is produced throughout a man's lifetime. The prostate converts testosterone to a more powerful androgen, dihydrotestosterone (DHT). DHT stimulates cell growth in the tissue that lines the prostate gland (the glandular epithelium) and is the major cause of the rapid prostate enlargement that occurs between puberty and young adulthood. DHT is a prime suspect in prostate enlargement in later adulthood.
- *Estrogen:* Some authorities believe that the female hormone estrogen may also play a role in BPH; some estrogen is always present in men. As men age, testosterone levels drop and the proportion of estrogen increases, this possibly triggering prostate growth.

**5.5 Growth factors:** - Deaver suggested in 1922 that prostatic enlargement is due to one or more internal secretions, substances produced by the prostate stimulate glandular or stromal proliferation. Subsequent work suggested that the presence of mitogen in the humans prostate, this mitogen is present in normal human prostate and BPH as well as in carcinomas of the prostate [11].

Obstructive symptoms	Irritative symptoms		
Urinary Stream: Gradual decrease in the force	Frequency: A decreased time between voiding		
of the stream. variable, weak and dribbling	is regarded as one of the irritative symptoms in men with BPH.		
Abdominal straining: with prostatism contract	Nocturia: awakening and voiding because of		
the abdominal muscles during voiding	the desire to void		
Hesitancy Less intravesical pressure needed for	Urgency and urge incontinence: It is a strong		
voiding in patient with outflow obstruction.	desire to void		
<b>Intermittency:</b> disruption of the urinary stream	<b>Dysuria</b> : painful voiding often as a feeling of		
during voiding	"passing broken glass "in the penile urethra of a		
	burning sensation		
Incomplete Bladder emptying: suprapubic	Urinary Tract infection: of lower tract		
discomfort after voiding	infection are pollakiuria, dysuria, super pubic		
	discomfort and burning, sensation in the pendulous		
<b>Terminal dribbling:</b> end flow is reduced to dribbling			

# 6. Symptoms of benign prostatic hyperplasia (BPH).

# 7. Diagnosis complaining of big prostate of BPH symptoms.

Men rarely come, but Men usually present with lower urinary tract infection (LUTS) of a complication from unrelieved bladder out flow obstruction.

Rapid estimation of these risks can be achieved by assessment incorporating;

- 1. History of symptoms, co morbidity and age
- 2. Careful examination of the prostate and lower abdomen
- 3. Prostate specific antigen in serum and urinary flow rate
- 4. Other tests.

# 7.1 History of symptoms, co morbidity and age.

History taking of intake of dietary fluids is useful. Frequency volume charts and input -output charts can identify simple changes in lifestyle that help symptoms very at little risk. A drugs history must be taken. Vasoactive agents can be lead to voiding difficult or retention by increasing stimulation of - adrenoceptors. A history of cardiovascular disease, particularly congestive cardiac failure, and a history of falling may indicate that -blockers drugs therapy is unwise. The presence and quality of sexual function should be defined. Social factors such as the need for normal outward ejaculation of fertility should be elucidated because of importance in relative younger men.

# 7.2 Careful examination of the prostate and lower abdomen.

A focused clinical examination should include:

- 2. Urine dipstick to exclude infection and hematuria
- 3. Looking for an distended bladder and sign of rectal impairment
- 4. Digital rectal examination of the pelvis to asses pelvic tone, prostate consistency and size.
- 5. Urinary flow rate

# 7.3 Other Tests

It is easy to examine upper urinary tract if large residual urine, palpable bladder by radiology or ultrasound. Information on prostatic volume will be evaluated by digital rectal examination and prostate specific antigen[1].

# 8. Management of BPH

Management of BPH has changed dramatically over the past decade. Surgical intervention (i.e. Trans urethral resection of the prostate [TURP] was the mainstay of treatment in the recent past for men with bothersome symptoms. The minimally invasive surgical treatment became even less invasive with introduction of laser inflicted destruction of prostatic tissue, transurethral incision of the prostate (TUIP), transurethral needle ablation (TUNA) and others. Pharmacological therapy is the preferred treatment today; 85 to 90 percent of cases are treated with medication. Pharmacological management has positive outcomes since the complications of BPH include acute urinary retention and symptom progression necessitating eventual surgery, can often be reduced or eliminated. The goal of therapy is to eliminate symptoms that interfere with daily activities thus enhancing quality of life [6]<sup>-</sup>

# 8.1 Pharmacological Intervention

Pharmacological intervention controls symptoms in majority of patients and involves two approaches:

1) Reducing the size of the prostate gland by blocking conversion of testosterone to DHT by 5-alpha reductase.

2) Antagonizing -adrenergic receptors within the gland to dilate smooth muscle surrounding the urethra [6].

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## 1) Treatments

## A) Lifestyle changes

Advice on lifestyle changes is useful for most men. Stopping smoking and altering the nature, volume and time of fluid intake may help significantly [6].

## **B) 5 reductase Inhibitors**

5 reductase prostate cells enzyme converts testosterone to dihydrotestosterone. This dihydrotestosterone acts on prostatic tissue to induce benign prostatic hyperplasia. 5 - reductase inhibitors decrease the production of dihydrotestosterone, thereby arresting prostatic hyperplasia.

Drugs and dose: - Finasteride: 5 mg once daily, Dutasteride: 0.5 mg once daily.

Side effects are:-Erectile dysfunction, Reduction of libido, Ejaculatory disorder, Gynaecomastia Breast tenderness.

Cautions: - Both Finasteride and dutasteride decrease serum concentration of prostate specific antigen by about a half and reference values need to be adjusted if patients is suspected of having or its being following up for prostate cancer [12].

# C) Alpha-adrenergic receptors antagonists

Activation of the <sup>1</sup> adrenoceptors causes contraction of the prostatic smooth muscle, and Inhibition of these receptors relaxes the muscle in the bladder outflow tract; this decreases urinary outflow resistance and helps to improve the symptoms. - antagonists are the first line treatment for BPH.

Drugs and dose Alfuzosin: 2.5 mg three times a day or 10 mg once a day (once daily preparation), Doxazosin: 1-8 mg once a day (usual maintenance dose 2-4 mg once day), Tamsulosin: 0.4 mg once a day (same dose for modified release formulation), Terazosin: 1-10 mg once a day (usual maintenance dose 5-10 mg once a day).

Side effects:-Postural hypotension, Headache, Dizzeness ,Somnolence. Abnormal ejaculation [12].

# **D)** Surgical treatments

Doctors recommended removal of the enlarged part of the prostate as the best solution for BPH Condition, only the enlarged tissues that is pressing against the urethra is removed, the rest of the inside tissues and outside capsule are left intact. The following section describes the type of surgery that is used.

# 1) Transurethral surgery

Procedure called transurethral resection of the prostate (TURP) is used for all prostatic surgeries. With TURP, an instrument called resectoscope is inserted through the penis. The resectoscope, which is about ½ inch in diameter and 12 inches long, contains valves, light, for controlling irrigating fluid, and an electric loop that cuts tissues and seals blood vessels.

## 2) Open surgery

When transurethral procedures cannot be used, then open surgery is option. Which requires an external incision. Open surgery is often done when the gland is greatly enlarged, when there are complicating factors, With all the open procedures, anaesthesia is given. Once the surgeon reaches the prostate capsule, they scoops out the enlarged tissues from the gland.

# 3) Laser surgery

Use of laser fibers was approved for surgical procedures. Nd: YAG lasers to vaporize obstruction prostate tissues. The doctor passes laser fiber through urethra into the prostate using a cystoscope and then delivers several bursts of energy lasting 30 to 60 seconds. The laser energy destroys prostate tissues and causes shrinkage [5].

## **9.** Alternative treatments

Several plants extracts have been reported to improve lower urinary tract symptoms due to BPH, these includes

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- Extracts of *Cucurbita pepo* (pumpkin) seeds.
- Extracts of *Urtica dioica* (stinging nettle) roots.
- Extracts of *Opuntia* (cactus) flowers.
- Extracts of Hypoxis rooperi (South African star grass)
- Extracts of *Pygeum africanum* (African plum tree).
- Extracts of *serenoa repens* (saw palmetto) berry.

Some studies suggested these that extracts are as effective as antagonist. However, the studies are often poorly designed, and the extracts have not undergone the same scrutiny as conventional drug for efficacy, purity and safety. The World Health Organisation (WHO) international consultation on urological diseases consensus group does not recommended treatments of these extracts until more robust evidence exists [13]

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