BPH

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Definition

- BPH is a histologic diagnosis that refers to the proliferation of glandular epithelial tissue, smooth muscle, and connective tissue within the prostatic transition zone, hence the term “stromo-glandular hyperplasia.”
- BPH is likely the result of a multifactorial process, the exact etiology of which is unknown.
- What is clearly necessary for the development of BPH, however, is the presence of functioning testes.

Etiology

- I) Hormones:
- 1) Androgens: Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty, and aging
- Patients castrated prior to puberty or who are affected by a variety of genetic diseases that impair androgen action or production do not develop BPH
- A nuclear membrane–bound enzyme *steroid 5α-reductase* converts testosterone into DHT, the principal androgen

Etiology

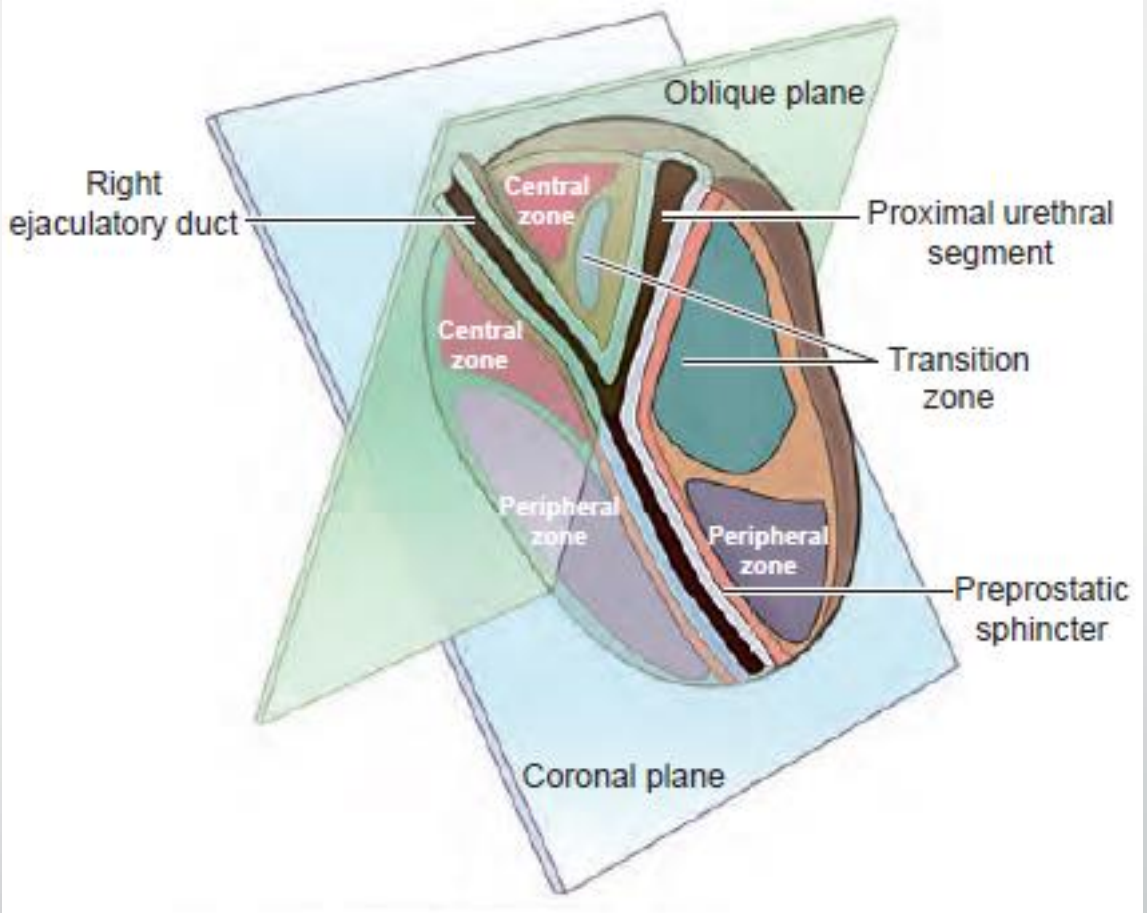
- I) Hormones:
- 2) Androgen Receptors (AR): The prostate, unlike other androgen-dependent organs, maintains its ability to respond to androgens throughout life
- Age related increases in estrogen may increase AR expression in the aging prostate
- Intra-prostatic DHT concentrations are maintained but not elevated in BPH
- Type 2 5α-reductase is the predominant prostatic 5α-reductase

Etiology

- II) Genetic and Familial Factors:
- approximately 50% of cases of men undergoing prostatectomy for BPH at less than 60 years of age could be attributable to an inheritable form of the disease
- Familial BPH was characterized by large prostate size, with a mean prostate volume of 82.7 mL in men with hereditary BPH compared with 55.5 mL in men with sporadic BPH

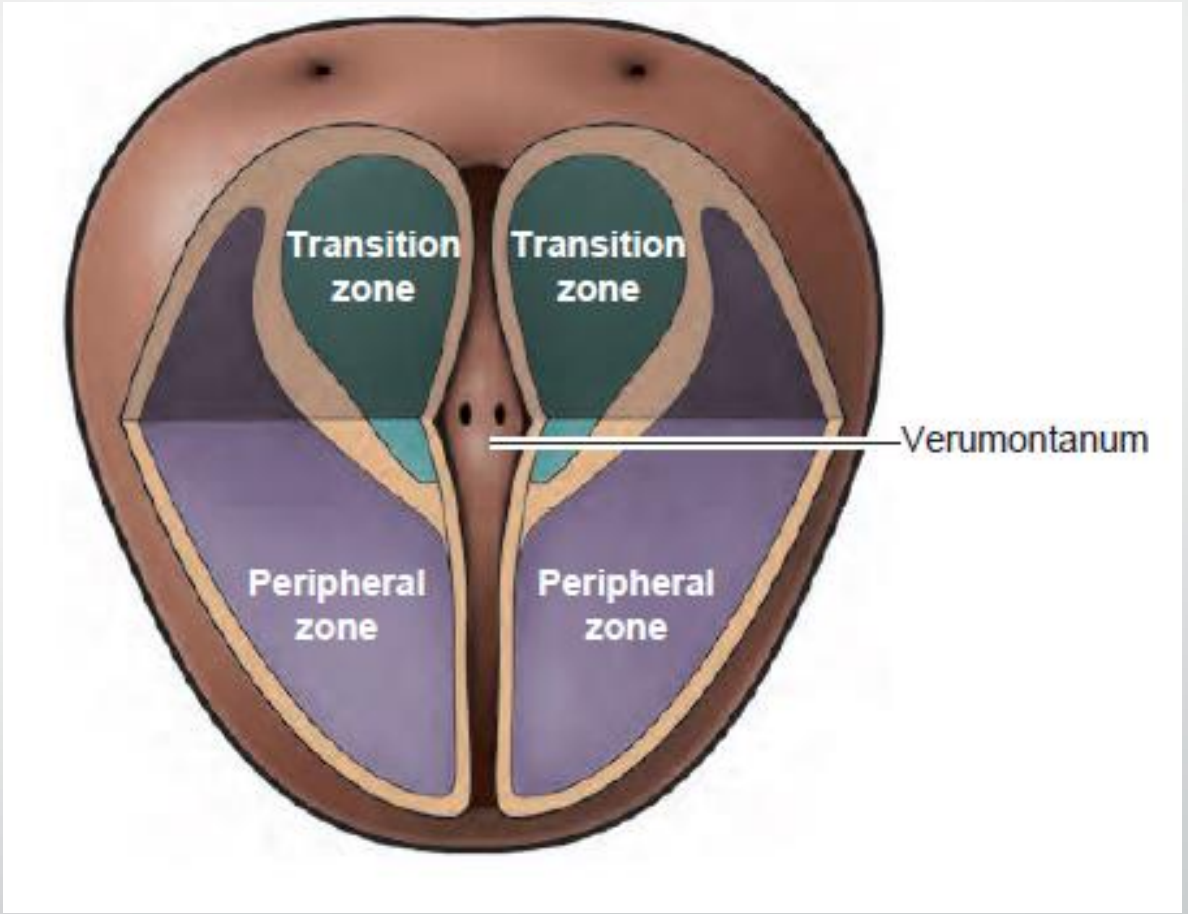
Pathophysiology: Anatomy

- BPH first develops in the periurethral transition zone of the prostate
- All BPH nodules develop either in the transition zone or in the periurethral region



Pathophysiology: Anatomy

- However, the transition zone also enlarges with age, unrelated to the development of nodules

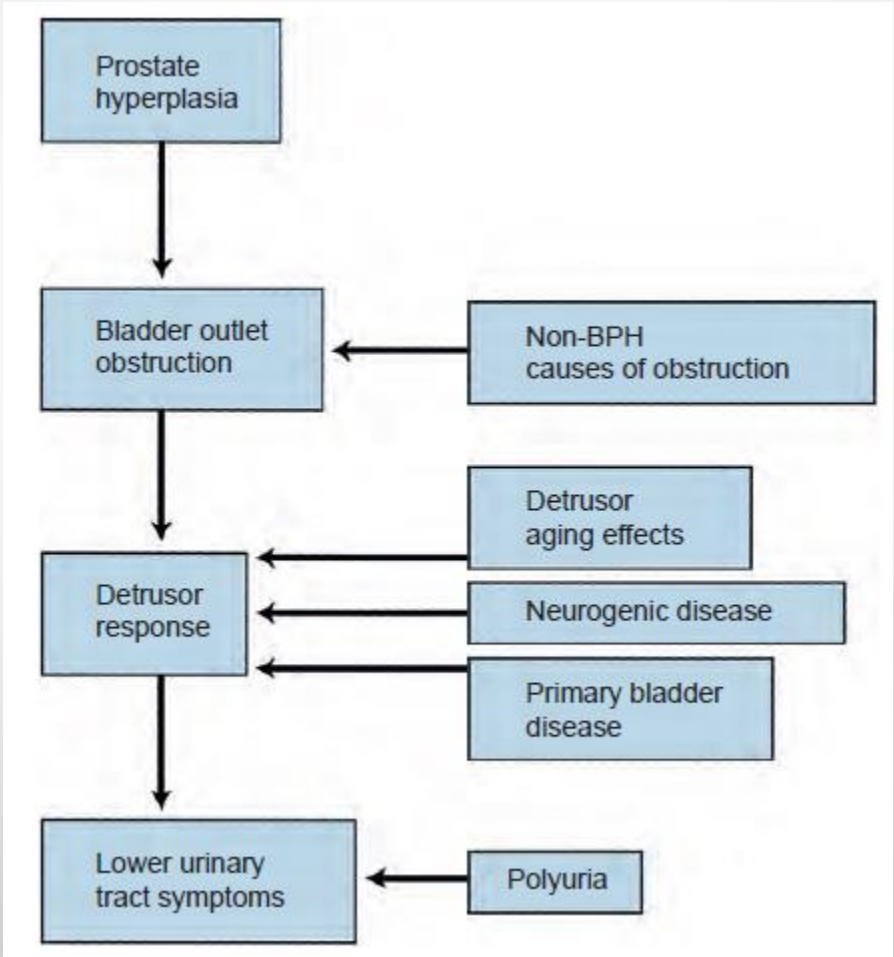


Pathophysiology: Anatomy

- The presence of the prostatic capsule plays an important role in the development of LUTS
- Prostatic hyperplasia increases urethral resistance, resulting in compensatory changes in bladder function
- Obstruction-induced changes in detrusor function, compounded by age-related changes in both bladder and nervous system function, lead to urinary frequency, urgency, and nocturia, the most bothersome BPH-related complaints

Pathophysiology

- The pathophysiology of benign prostatic hyperplasia (BPH) involves complex interactions between urethral obstruction, detrusor function and dysfunction, and urine production



Pathophysiology: Histologic Features

- Early periurethral nodules are purely stromal in character but transition zone nodules represent proliferation of glandular tissue
- This proliferative process leads to a tight packing of glands within a given area as well as an increase in the height of the lining epithelium.
- There appears to be hypertrophy of individual epithelial cells as well

Pathophysiology: Histologic Features

- During the first 20 years of BPH development, the disease is predominantly characterized by an increased number of nodules
- Then a second phase of evolution occurs in which there is a significant increase in large nodules and the size of glandular nodules clearly predominates
- Both passive and active forces (i.e. smooth muscles) in prostatic tissue play a major role in the pathophysiology of BPH

Pathophysiology: Histologic Features

- Adrenergic nervous system stimulation clearly results in a dynamic increase in prostatic urethral resistance. Blockade of this stimulation by α-receptor blockers clearly diminishes this response
- α1A is the most abundant adrenoreceptor subtype present in the human prostate
- type 4 and type 5 phosphodiesterase isoenzymes in the prostate and the detrusor muscle of the bladder implies that phosphodiesterase inhibitors is appropriate therapies for BPH-related LUTS

Prevalence and Terms

- Autopsy proven histological prevalence increases starting at age 40-45 years to reach 60% at age 60 and 80% at age 80
- BPE: benign prostatic enlargement
- BPO: benign prostatic Obstruction
- It is important to realize that not all men with BPE will develop obstruction or BPO, just as not all men with BPH will have BPE

Prevalence and Terms

- BOO: Bladder Outlet Obstruction
- Obstruction may also be caused by other conditions referred to as BOO. Thus, BPO is a subset of BOO
- The enlarged gland has been proposed to contribute to the male LUTS complex via at least two routes:
- 1. Direct BOO/BPO from enlarged tissue (static component)
- 2. Increased smooth muscle tone and resistance within the enlarged gland (dynamic component)

Prevalence and Terms

- LUTS are non-specific, occur in men and women with similar frequency and may be caused by many conditions, including BPE and BPO
- Complications: Urinary Tract Infections, Bladder Stones, Urinary Incontinence, Upper Urinary Tract Deterioration and Azotemia, Hematuria, Acute urinary retention (AUR), Bladder Decompensation (CUR).

Initial Evaluation (History)

- I) Complete Medical History: to assess symptoms, prior procedures that could explain the symptoms, sexual history, use of medications, and overall fitness and health.
- history of hematuria, UTI, diabetes, nervous system disease (e.g., Parkinson disease or stroke), urethral stricture disease, urinary retention, and aggravation of symptoms by cold or sinus medication
- Over-the-counter medications: drugs that impair bladder contractility (anticholinergics) or that increase outflow resistance (sympathomimetics)
- The IPSS, a validated self-administered questionnaire, can provide clinicians with information regarding the symptom burden patients are experiencing

IPSS questionnaire

Over the past month, how often have you…	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	YOUR SCORE
1. …had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2. …had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. …stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. …found it difficult to postpone urination?	0	1	2	3	4	5	
5. …had a weak urinary stream?	0	1	2	3	4	5	
6. …had to push or strain to begin urination?	0	1	2	3	4	5	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	Once	Twice	3 times	4 times	5 times or more	
						TOTAL	

8. QUALITY OF LIFE DUE TO URINARY SYMPTOMS
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?

Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied & dissatisfied	Mostly dissatisfied	Unhappy	Terrible
0	1	2	3	4	5	6

Initial Evaluation (History & P/E)

- Bladder diary and frequency-volume chart: identify patients with polyuria
- II) P/E:
- a) DRE: detect prostate or rectal malignancy, to evaluate anal sphincter tone, presence of induration, the presence of a nodule, & establishes the approximate size of the prostate gland;
- b) Focused neurologic examination;
- c) Examination of the external genitalia (e.g. meatal stenosis);
- d) Abdominal examination is necessary (palpation + percussion)

Initial Evaluation (Work up)

- III) Labs:
- 1. Urinalysis: to rule out other causes of LUTS (bacteria, blood, white cells, glucose, or protein)
- 2. Serum Creatinine Measurement: Optional to exclude renal insufficiency caused by the presence of obstructive-uropathy
- 3. Serum Prostate-Specific Antigen (PSA)

Initial Evaluation (Work up)

- III) Labs:
- 4. optional studies: PVR, uroflowmetry, and pressure flow studies:
- A) A PVR can be useful in determining a baseline ability of the bladder to empty, detecting severe urinary retention that may not be amenable to medical therapy, and/or indicate detrusor dysfunction
- B) Uroflowmetry: simple and risk-free, office-based procedure: Flow rates of <10 mL/s have shown a specificity of 70%/ sensitivity of 47% for BOO
- C) Pressure flow studies: If the patient's condition is not sufficiently suggestive of obstruction (e.g., peak urinary flow [Q_{max}] >10 mL/sec)

Medical Therapy

- I) Alpha Blockers: in moderate to severe LUTS/BPH: alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin
- They are equally effective in terms of IPSS improvement, with an expected range of improvement of 5-8 points
- The choice of specific agent should consider the differing adverse events profiles of each:
- Terazosin and doxazosin, are non-specific alpha-1 receptor blockers that are both approved for the treatment of hypertension
- Tamsulosin, alfuzosin, and silodosin have lower potential to cause orthostatic hypotension and syncope

Medical Therapy

- I) Alpha Blockers:
- Only two are alpha 1a selective: tamsulosin (10:1) and silodosin (161:1) those drugs are more selective for the alpha 1a versus the alpha 1b receptor; are more prone to induce Ejaculatory dysfunction (Anejaculation) (Silodocin > tamsulosin); But less hypotensive effects.
- Younger sexually active men are more likely to discontinue due to EjD; therefore, it would be prudent to select alpha blockers with a low incidence of EjD
- Patients on several antihypertensives, or with orthostatic hypotension, it is best to select an alpha blocker that exhibits minimal impact on blood pressure (e.g., the highly selective alpha 1a blocker silodosin)

Medical Therapy

- II) 5-Alpha Reductase Inhibitor (5-ARI):
- Both testosterone and DHT bind to the androgen receptor, although DHT does so with greater affinity and is thus considered to be the more potent androgenic steroid hormone.
- The T/DHT-androgen receptor complex within the nucleus of the cells of the prostate initiates transcription and translation, thus promoting cellular growth
- 5-ARIs act via inhibition of 5AR, leading to less available DHT in the prostate
- This, in turn, leads to a reduction in the overall androgenic growth stimulus in the prostate, an increase in apoptosis and atrophy, and ultimately a shrinkage of the organ ranging from 15-25% measured at six months

Medical Therapy

- II) 5-Alpha Reductase Inhibitor (5-ARI):
- The atrophy is most pronounced in the glandular epithelial component of the prostate, which is the source of the production and release of serum PSA.
- Serum PSA drop by approximately 50% (and a concomitant decrease in serum free PSA by 50%, which means that the ratio of free/total PSA remains constant)
- The indication for treatment with 5-ARIs depends on prostate volume and PSA threshold: Ultrasonic prostate size of >30 cc can achieved significant results, & a minimum threshold PSA 1.5ng/dL is preferred.

Medical Therapy

- II) 5-Alpha Reductase Inhibitor (5-ARI):
- In the prostate, and specifically in BPH tissue, type II 5-AR is far more common than type I
- A) Finasteride: exclusively inhibits the 5-AR type II isoenzyme, reduce serum levels of DHT by 70%, in prostate tissues by 80%, & IPSS improvements of 3-4 points
- B) Dutasteride: inhibits both types I and II, reduce serum DHT by 95%,in prostate tissues by 94%, & IPSS improvements of ~4.5 points
- 5-ARIs alone or in combination with alpha blockers are recommended to prevent progression of LUTS/BPH, reduce the risks of urinary retention and need for future prostate-related surgery

Medical Therapy

- II) 5-Alpha Reductase Inhibitor (5-ARI):
- Side Effects: (-ve)
- A) Sexual Dysfunction: ED, libido disturbances, and ejaculatory problems
- B) Gynecomastia and breast tenderness
- C) lower risk of prostate Ca but tendency to have higher grade cancer
- +ve: reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH.
- III) Phosphodiesterase-5 Inhibitor (PDE5): irrespective of comorbid ED

Medical Therapy

- III) Combination Therapy
- A) 5-ARI in combination with an alpha blocker to patients with LUTS associated with demonstrable prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a PSA >1.5ng/dL, or palpable prostate enlargement on DRE
- B) Anticholinergic agents with an alpha blocker, to patients with moderate to severe predominant storage LUTS
- Do not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone

Surgical Therapy

- Indications:
- renal insufficiency secondary to BPH,
- refractory urinary retention secondary to BPH,
- recurrent urinary tract infections (UTIs),
- recurrent bladder stones or gross hematuria due to BPH, and/or
- with LUTS/BPH refractory to or unwilling to use medical therapies

Surgical Therapy

- I) TURP: remains the historical standard by which all other subsequent surgical approaches to treatment of BPH are compared
- Successful TURP can relieve symptoms quickly with most men experiencing significantly stronger urine flow within days of the procedure
- The risk of complications (e.g., bleeding, transfusion, hyponatremia, TURP syndrome, death) increase with increasing prostate size and increased duration of resection
- II) Open, laparoscopic, or robotic assisted prostatectomy, only in patients with large (80-150 gm) to very large prostates (>150 gm)

Surgical Therapy

- III) Transurethral Incision of the Prostate (TUIP): for patients with prostates ≤30cc as a surgical treatment of LUTS/BPH, lower rates of Retrograde Ejaculation and need for blood transfusion than TURP.
- IV) Prostatic Urethral Lift (PUL): placement of transprostatic suture implants. The implants pull the lumen of the prostatic urethra towards the capsule and widen the prostatic urethral lumen
- +ve: preservation of erectile and ejaculatory function
- -ve: only average size prostate (30-80 gm), and no obstructive middle lobe of prostate

Surgical Therapy

- V) Laser Enucleation:
- Holmium laser enucleation of the prostate (HoLEP) or thulium laser enucleation of the prostate (ThuLEP): prostate size-independent options for the treatment of LUTS/BPH
- Better coagulative properties in tissue than TURP (i.e. less bleeding)
- Minimal tissue depth penetration with both holmium and thulium (0.4mm for holmium, 0.2 mm for thulium)
- Similar outcomes when compared to TURP for the treatment of symptomatic BPH as measured by IPSS and IPSS-QoL outcomes

Surgical Therapy

- VI) Rezum procedure:
- sterile water vapor (steam) that is injected into the enlarged portions of the prostate. The steam causes the prostate cells that are responsible for the enlargement to die, which then leads to shrinking of the prostate.
- Adv.: Clinic based procedure, minimal adverse events.
- Disadv.: Sx improvement up to 2 years, high postop AUR, & only for average sized prostates (30-80gm).

Thank You