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BENIGN PROSTATIC HYPERPLASIA(BPH)

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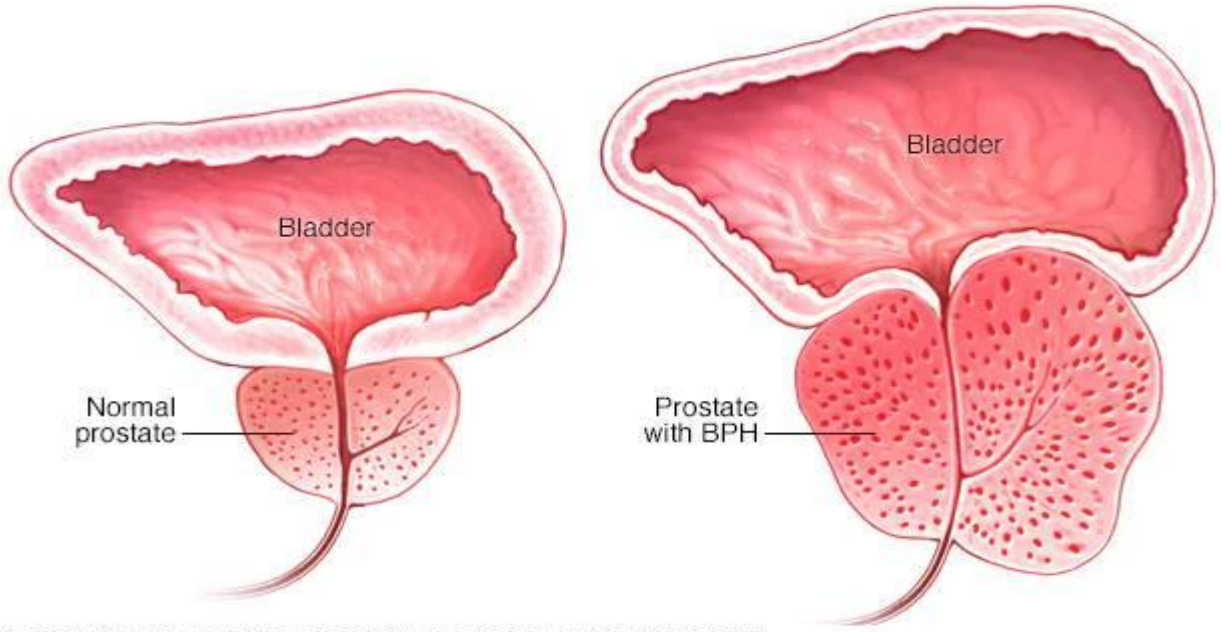
❖ INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common diseases, and its incidence has accelerated recently. BPH usually occurs in men in their 50s, and 80% of men in their 70s suffer from BPH-related lower urinary tract symptoms (LUTS) [1]. Although BPH is not a fatal disease, the morbidity from BPH and its potential risk of complications diminishes quality of life (QoL) and causes huge social financial problems [2,3]. BPH-related LUTS are a consequence of dynamic and static obstruction. In the past, age, genetics, and testosterone were regarded as the primary causes of prostate enlargement, but recently, food, exercise, lifestyle, and metabolic syndrome have been recognized as other major causes of BPH and have been widely researched [4]. There have been many changes in the treatment pattern of BPH. Alpha-blockers and 5-alpha reductase inhibitors are becoming the first-line treatment option owing to their excellent efficacy and convenience of administering without severe adverse effects. Laser surgery as a substitute for previous BPH surgery such as transurethral resection of the prostate (TURP) and open prostatectomy has also been attempted. Several research studies on etiologies and treatment options have been published from various preclinical and clinical aspects. This article presents the scientific foundation of prostate enlargement and some reports about innovative trials of BPH therapy.



❖ Epidemiology

Epidemiology of benign prostatic hyperplasia (BPH) is incompletely understood. The following study was done to estimate the prevalence of BPH according to obstructive and irritative symptoms of prostate obstruction determined by uroflowmetry and prostate size. In a cross-sectional study a total of 8,466 men aged 40 or older were interviewed by 74 general practitioners and answered the International Prostate Symptom Score (I-PSS) questionnaire.

The subjects were randomly identified from 30 counties of Iran. They were invited to have a digital rectal examination (DRE), serum total prostate-specific antigen (tPSA) assay, abdominal ultrasonography to measure prostate size and measurement of maximum urinary flow rate (Qmax).

Data on medical history, toxic habits, and current use of medications were obtained. Of the men interviewed, the prevalence of BPH, defined as I-PSS greater than 7, maximum flow less than 15 ml/s and prostate size greater than 30 gm, was 23.8%.

The prevalence increased with age, from 1.2% in men 40-49 to 36% in those >70 years (tested for trend, P = 0.001). A positive association was found between BPH and body mass index (BMI) (P = 0.04), height (P = 0.03), diabetes mellitus (P = 0.04), increased total energy intake (P = 0.02), age-adjusted levels of total PSA (P = 0.02), heart disease (P = 0.03), and marital status (P = 0.01). The prevalence of BPH is relatively high in Iran.

The provided bothersome due to BPH did not correlate to symptom severity and should be considered independently in clinical decision-making.

Etiology And Risk Factor:-

The etiology of BPH is not completely understood, but it seems to be multifactorial and endocrine controlled. The ,prostate is composed of both stromal and epithelial elements and each, either alone or in combination, can give rise to hyperplastic nodules and the symptoms associated with BPH. Each element may be targeted in medical management schemes.

Observations and clinical studies in men have clearly demonstrated that BPH is under endocrine control. Castration results in the regression of established BPH and improvement in urinary symptoms. Additional investigations have demonstrated a positive correlation between levels of free testosterone and estrogen and the volume of BPH.
The latter may suggest that the association between aging and BPH might result from the increased estrogen ,levels of aging causing induction of the androgen receptor .which thereby sensitizes the prostate to free testosterone There is evidence that estrogens acting through stromal ,and epithelial estrogen receptors may contribute, in part to diseases of the prostate. Genetic or environmental factors that influence 5α-reductase appear to be important in the development of BPH as well
Other risk factor include:-

A-Hormones
Most experts consider androgens (testosterone and related hormones) to play a permissive role in the development of BPH. This means that androgens must be present for BPH to occur, but do not necessarily directly cause the problems
2-Diet:-Studies indicate that dietary patterns may affect development of BPH, but further research is needed to clarify any important relationship. Studies from China suggest that greater protein intake may be a factor in development of BPH
C-degeneration
Benign prostatic hyperplasia is an age-related disease. Misrepair-accumulation aging theory suggests that development of benign prostatic hyperplasia is a consequence of fibrosis and weakening of the muscular tissue in the prostate

Pathology

As discussed earlier, BPH develops in the transition zone. It is truly a hyperplastic process resulting from an increase in cell number. Microscopic evaluation reveals a nodular growth pattern that is composed of varying amounts of stroma and epithelium.

Stroma is composed of varying amounts of collagen and smooth muscle. The differential representation of ,the histologic components of BPH explains, in part the potential responsiveness to medical therapy

Pathophysiology

Increase urethral pressure lead to bladder wall hypertrophy so First : the changes that lead to decrease compliance causing frequency and urgency Second :changes associated with decreased contractility causing decrease force of urinary stream,hestancy,intermittency and increase residual volume

❖ Symptoms

The severity of symptoms in people who have prostate gland enlargement varies, but symptoms tend to gradually worsen over time.

- Common signs and symptoms of BPH include:

Frequent or urgent need to urinate
Increased frequency of urination at night (nocturia)
Difficulty starting urination
Weak urine stream or a stream that stops and starts
Dribbling at the end of urination
Inability to completely empty the bladder

- Less common signs and symptoms include:

Urinary tract infection
Inability to urinate
Blood in the urine

The size of your prostate doesn't necessarily determine the severity of your symptoms. Some men with only slightly enlarged prostates can have significant symptoms, while other men with very enlarged prostates can have only minor urinary symptoms.

In some men, symptoms eventually stabilize and might even improve over time. (1)

❖ Investigations

Urine flow study: During this test, the patient voluntarily empties his bladder and the amount of flow is measured. A special device can help physicians detect reduced urine flow associated with BPH.

Digital rectal examination (DRE): The physician inserts a gloved finger into the rectum (located next to the prostate) and feels the back of the prostate. Prostate cancers can sometimes be detected as lumps or bumps on the prostate here.
Prostate-specific antigen (PSA) blood test: Elevated levels of PSA in the blood may sometimes be an indicator of prostate cancer.

Cystoscopy: In this examination, the physician inserts a thin tube with a tiny camera on the end called a cystoscope through the opening of the urethra at the tip of the penis. The camera allows the physician to inspect the inside of the prostate, urethra channel and bladder.

Transrectal ultrasound and Prostate Biopsy: There are two potential reasons for this exam:

(1) If there is suspicion for prostate cancer, this test may be recommended. The physician uses an ultrasound probe to acquire images of the prostate and guides a biopsy needle into the prostate to remove small slivers of tissue for examination under a microscope.

(2) Your doctor may simply want to know the exact size of your prostate to plan prostate surgery for BPH. In this case, only an ultrasound image will be obtained; no needles will be used.

Transabdominal ultrasound: This exam may be performed to measure the size of the prostate and the amount of urine left in the bladder after urination.
Prostate magnetic resonance imaging (MRI): MRI provides views of the entire prostate with excellent soft tissue contrast. (2)

❖ Treatment

After patients have been evaluated, they should be informed of the various therapeutic options for BPH. It is advisable for patients to consult with their physicians to make an educated decision on the basis of the relative efficacy and side effects of the treatment options.Specific treatment recommendations can be offered for certain groups of patients. For those with mild symptoms (IPSS score, 0–7), watchful waiting is generally advised. On the other end of the therapeutic spectrum, absolute surgical indications include urinary retention refractory to medical management and attempts at catheter removal, recurrent urinary tract infection, recurrent gross hematuria, bladder stones, renal insufficiency, or large bladder diverticula.

A. Watchful Waiting

Very few studies on the natural history of BPH have been reported. The risk of progression or complications is uncer-tain. However, in men with symptomatic BPH, it is clear that progression is not inevitable and that some menundergo spontaneous improvement or resolution of their symptoms.

Retrospective studies on the natural history of BPH are inherently subject to bias, related to patient selection and the type and extent of follow-up. Very few prospective studies addressing the natural history of BPH have been reported.

A large randomized study compared finasteride with placebo in men with moderately to severely symptomatic BPH and enlarged prostates on DRE . Patients in the placebo arm of the study had a 7% risk of developing urinary retention over 4 years. As mentioned earlier, watchful waiting is the appropriate management of men with mild symptom scores (0–7). Men with moderate or severe symptoms can also be managed in this fashion if they so choose. Neither the optimal interval for follow-up nor specific end points for intervention have been defined.

B. Medical Therapy

1. AlphaBlockers

The rationale for blocker therapy in BPH As described earlier, BPO is caused partly by α1-adrenoceptor-mediated prostatic smooth muscle contraction, and this is the rationale for α- adrenoceptor blocker treatment

for symptomatic BPO.There are two broad subtypes of α-adrenoceptor (AR)—α1 and α2.
Molecular cloning studies have identified three α1-AR subtypes—α1a (pre-dominant in human stroma and therefore mediates prostate smooth muscle contraction), α1b (predominant in human prostate epithelium), and α1L(believed to be a conformational state of the α1a-AR). The AR subtypes mediating the efficacy and side effects of α-adrenoceptor-blocking drugs are unknown.
Alpha-blocker classification α-blockers are categorized by their selectivity for the AR and by their elim-ination half-life.

• Non-selective: phenoxybenzamine—effective symptom control, but high side effect profile.
• α1: prazosin, alfuzosin, indoramin.
• Long-acting α1: terazosin, doxazosin, alfuzosin sustained release (SR).
• Subtype selective: tamsulosin—relatively selective for the α1a-AR subtype, compared to the α1b subtype.

No study has directly compared one α-blocker with another in terms of efficacy or side effects. Terazosin and doxazosin require dose titration to minimize dizziness and syncope at the start of treatment.
Indications for treatment Bothersome LUTS where WW has failed or the patient wishes to have treatment.

Efficacy Percentage of patients who respond to alpha-blockers
Patients are able to perceive a 4-point improvement in IPSS. If 'response' is defined as >25% improvement in symptoms, relative to placebo, most studies describe response rates of 30–40%.The mean probability for im-
For those men who respond, α-blockers have a much more rapid onset than do 5ARIs. Their effect will be maximal within a month of starting treatment.

2. 5A-Reductase inhibitors—Finasteride is a 5α-reductase inhibitor that blocks the conversion of testosterone to dihy- drotestosterone (DHT). This drug affects the epithelial com-ponent of the prostate, resulting in a reduction in the size of the gland and improvement in symptoms. Six-month ther-apy is required to see the maximum effects on prostate size (20% reduction) and symptomatic improvement. Several randomized, double-blind, placebo-controlled trials have compared finasteride with

placebo. Efficacy, safety, and durability are well established. However, symp-tomatic improvement is seen only in men with enlargedprostates (>40 cm3).
Side effects are uncommon and include decreased libido, decreased ejaculate volume, and impo-tence. Serum PSA is reduced by approximately 50% in patients being treated with finasteride, but individual values may vary.
Dutasteride differs from finasteride as it inhibits both iso- enzymes of 5α-reductase. Similar to finasteride, it reduces serum PSA and total prostate volume. Randomized, placebo-controlled trials have shown the efficacy of dutasteride in symptomatic relief, symptoms scores, peak urinary flow rate,and reduced risk of acute urinary retention and the need for surgery. Side effects are relatively uncommon and include erectile dysfunction, decreased libido, gynecomastia, and ejaculation disorders. Few studies comparing finasteride and dutasteride head-to-head. One retrospective analysis of >5000 men older than 65 years treated with 5α-reductase inhibitors in the mid-2000s found small but statistically sig-nificantly differences, with rates of urinary retention of 12% and 14.7% for dutasteride and finasteride, respectively (p =0.0042), and rates of prostate surgery of 3.9% and 5.1%, respectively (p = 0.03).

3. Combination therapy—The first randomized, double- blind, placebo-controlled study investigating combination α-blocker and 5α-reductase inhibitor therapy was a four- arm Veterans Administration Cooperative Trial comparing placebo, finasteride alone, terazosin alone, and combina-tion finasteride and terazosin .
More than 1200 patients participated, and significant decreases in IPSS and increases in urinary flow rates were seen only in the arms containing terazosin. However, one must note that enlarged prostates were not an entry criterion;
in fact, prostate size in this study was much smaller than that in previous controlled trials using finasteride (32 vs52 cm3). McConnell and colleagues conducted a long- term, double-blind trial involving 3047 men to compare the effects of placebo, doxazosin, finasteride, and combi-nation therapy on measures of the clinical progression of BPH (McConnell et al, 2003). The risk of overall clinical progression—defined as an increase above baseline of at least four points in the IPSS, acute urinary retention, uri-nary incontinence, renal insufficiency, or recurrent urinary tract infection—was significantly reduced by doxazosin (39% risk reduction)

and finasteride (34% risk reduction), as compared with placebo. The reduction in risk associ-ated with combination therapy (66% risk reduction) was significantly greater than that associated with doxazosin or finasteride alone. Patients most likely to benefit from com- bination therapy are those in whom baseline risk of pro-gression is very high, generally patients with larger glands and higher PSA values.

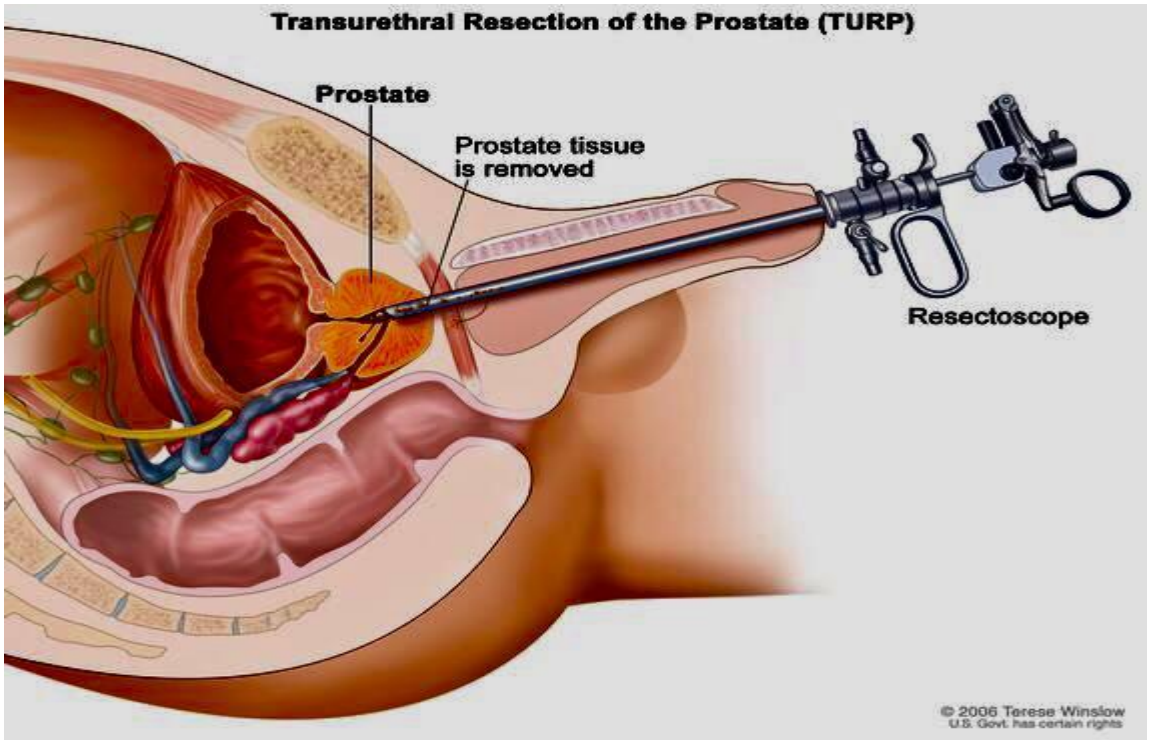
4. Phytotherapy—Phytotherapy refers to the use of plants or plant extracts for medicinal purposes. The use of phyto- therapy in BPH has been popular in Europe for years, and its use in the United States is growing as a result of patient- driven enthusiasm. Several plant extracts have been popu-larized, including the saw palmetto berry (Serenoa repens), the bark of Pygeum africanum, the roots of Echinacea pur-purea and Hypoxis rooperi, pollen extract, and the leaves of the trembling poplar. S. repens has been the most well-studied agent, usually at 320 mg/day. Given the poor regula-tion of the nutritional supplement industry, actual tablet content may vary extremely from the dose noted on theproduct label .
A prospective, randomized clinical trial of saw palmetto showed no benefit beyond pla-cebo for either IPSS improvement or urinary flow rate .
An updated systematic review including this and other trials confirmed no improvement over placebo for this approach

C.Surgical Therapy

1. Transurethral resection of the prostate—The vast majority of subtotal prostatectomies undertaken for BPH can be completed endoscopically. Most of these procedures involve the use of a spinal or general anesthetic and usually require an overnight hospital stay. Magnitude and durabil- ity of IPSS and flow rate improvement with transurethral resection of the prostate (TURP) is superior to that of any minimally invasive therapy. However, the length of hospital stay of patients undergoing TURP is greater.

Risks of TURP include retrograde ejaculation (75%), impotence (5–10%), and incontinence (<1%). Complications include bleeding; urethral stricture or bladder neck contracture; perforation of the prostate capsule with extravasation; and, if severe, transurethral resection (TUR) syndrome resulting from a hypervolemic, hyponatremic state due to absorption of the hypotonic irrigating solution. Clinical manifestations of the TUR syndrome include

nausea, vomiting, confusion, hypertension, bradycardia, and visual disturbances. The risk of the TUR syndrome increases with resection times >90 minutes and is usually seen in older men. Treatment includes diuresis and, in severe cases, hyper- tonic saline administration. TURP can now be performed with a bipolar electrode, allowing resection to be performed under saline irrigation. This approach eliminates the hypo-natremia responsible for TUR syndrome, though significant fluid volume absorption can still occur with prolonged resection.



2. Transurethral incision of the prostate—Men with moderate to severe symptoms and a small prostate often have posterior commissure hyperplasia (elevated bladder neck). These patients will often benefit from an incision of the prostate.
   This procedure is more rapid and less morbid than TURP. Outcomes in well-selected patients are comparable, although a lower rate of retrograde ejaculation with trans-urethral incision has been reported (25%).
   The technique involves two incisions using the Collins knife at the 5- and 7-o'clock positions. The incisions are started just distal to the ureteral orifices and are extended outward to the veru-montanum.

3. Transurethral vaporization of the prostate (TUVP)—Increasingly popular in recent years, ablative techniques use photo- or electroevaporation to ablate obstructing prostate tissue. The two most commonly used devices for these proce-dures are the neodymium-doped yttrium-aluminum-garnet (Nd:YAG) KTP "GreenLight" laser, which is preferentially absorbed by hemoglobin, and the plasma vaporization "Button" electrode. The latter works with a standard con- temporary bipolar generator used for bipolar TURP.

As with modern TURP, these procedures are performed under saline irrigation. The goal of the procedure in either case is to produce a central prostate defect comparable with what would be expected after a traditional TURP, but with less bleeding and lower risk of perforation.
The potential downsides are greater irritative voiding symptoms in the short term after the procedure and less durability of the result than a standard TURP. Also, as tissue is destroyed rather than resected, no specimen is sent to pathology for review.

4. Holmium laser enucleation of the prostate (HoLEP)-Rather than progressive resection or ablation of tissue from the urethra outward as with TURP and its derivatives, HoLEP denotes an anatomic dissection in the plane between the cen- tral and peripheral zones of the prostate. This approach is felt to provide the largest defect and perhaps the longest durabil-ity, but entails a longer learning curve than TURP or TUVP.

Simple (subtotal) prostatectomy—When the prostate is too large to be removed endoscopically, an open enucle-ation is necessary. What constitutes "too large" is subjec-tive and will vary depending upon the surgeon's experience with TURP. Glands >100 g are usually considered for open enucleation.

Open prostatectomy may also be initiated when concomitant bladder diverticulum or a large bladder stone is present or if dorsal lithotomy positioning is not possible. Open prostatectomies can be done with either a suprapu-bic or retropubic approach.

A simple suprapubic prostatec- tomy is performed transvesically and is the operation of choice in dealing with concomitant bladder pathology. After the bladder is opened, a semicircular incision is made in the bladder mucosa, distal to the trigone. The dissection plane is initiated sharply, and then blunt dissection with the finger is performed to remove the adenoma. The apical dissection should be done sharply to avoid injury to the distal sphinc-teric mechanism.

After the adenoma is removed, hemostasis is attained with suture ligatures, and both a urethral and a suprapubic catheter are inserted before closure. In a simple retropubic prostatectomy, the bladder is not entered. Rather, a transverse incision is made in the surgical capsule of the prostate, and the adenoma is enucleated as described earlier.
Only a urethral catheter is needed at the end of the proce-dure. Robot assisted simple prostatectomy has been reported in recent small series.

6. Transurethral microwave thermotherapy—Microwave hyperthermia is most commonly delivered with a transure-thral catheter.
Some devices cool the urethral mucosa to decrease the risk of injury. However, if temperatures are not >45°C, cooling is unnecessary.
Improvement in IPSS and flow rate has been documented, but as these procedures are done in the office with no visual verification of tissue abla-tion, results have been mixed.
Strong financial incentives, however, have driven frequent utilization in certain clinical contexts. Very sparse prospective data are available to fairly com-pare any of the above procedures with TURP or with each other.
A recent meta-analysis found few differences, but the component studies tended to be small and with limited follow-up .

All of the newer procedures aremore expensive than TURP, and comparative cost-effectiveness studies are sorely needed.

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