

Review Article

Benign Prostatic Hyperplasia: Review and Update on Etiopathogenesis and Treatment Modalities

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Abstract

Benign Prostatic Hyperplasia (BPH) is a major health problem for male above 50 years and increasing of age. It leads to different lower urinary tract problems including urgency, frequency, incomplete voiding and residual urine, recurrent Urinary tract Infection(UTI) etc and may even progress to prostatic cancer in some cases. The major cause of this BEP is proliferation of prostate smooth muscle, glands due to activation of metabolite of male hormone 5 Di Hydroxy Testosterone(DHT). Other risk factors include increasing age, genetic factors, obesity, excess testosterone, inflammation, trace elements zinc, vitamin D etc. The treatment modalities include alpha adrenergic, anti DHT drugs, laser therapy and Trans Urethral Resection of Prostate (TURP). These measures lead to improve qualities of many patients but no improvement or even worse in others. Review of literatures highlighted some important risk factors, some at molecular level, combined alternative drug management for BPH and molecular mechanism involved in BEP. Hopefully these will lead to a better understanding of etiopathology of BEP, treatment modalities and open research avenues to define better preventive strategies for management of BEP.

ABBREVIATIONS

BPH: Benign Prostatic Hyperplasia; UTI: Urinary Tract Infection; TURP: Trans Urethral Resection of Prostate; DHT: Di Hydroxy Testosterone; LUTS: Lower Urinary Tract Symptom; BPH: Benign Prostatic Hyperplasia; IPSS: International Prostate Symptoms Score; QOL: Quality of Life; VRU: Volume of Residual Urine; BOO: Bladder Out Let Obstruction; PKRP: Plasma Kinetic Resection of Prostate; HoLEP: Holorium Laser Nucleation of Prostate; ANO1 : Anoctamin 1; Pca: Prostate Cancer; HGPIN: Highgrade Prostatic Intraepithelial Neoplasm; CAM: Cell Adhesion Molecules; NH: Nodular Adenomatous Hyperplasia; HFD: High Fat Diet; ROS: Reactive Oxygen Species; INOS: Inducible Nitric Oxide; PVP: Greenlight Photoselective Vaporisation of Prostate; Cacc: Calcium Activated Chloride Channel; AR: Androgen Receptor; SRD5A₂: Steroid 5 Reductase Type II; IHC: Immunohistochemical; 5ARI: 5areductase Inhibitors; IGF: Pusulin Like Growth Factor; GL-PVP-Green Light Photo Selective Vaporization; TURS: Transurethral Resection Syndrome; ED: Erectile Dysfunction; PSA: Prostate Specific Antigen.

INTRODUCTION

Benign prostatic hyperplasia is a common disease of the ageing male population significantly impact quality of life

by causing lower urinary tract symptoms [1,2]. The affected individuals often accompanied by metabolic syndromes. Urinary symptoms may be microscopic, macroscopic, symptomatic, and asymptomatic. Up to 15-25% of men aged 50-65 years have lower urinary tract symptoms [3]. The current pathophysiological view emphasizes the role of genetic predisposition, hormonal dysregulation, locally released in the prostate growth factors action and a complex inflammatory BPH-associated process with the release of a number of pro-proliferative mediators. The current BPH pharmacotherapy involves administration of α -1-blockers, 5- α -reductase inhibitors, anti muscarinic drugs (cholinolytics) and phosphodiesterase-5-inhibitors, laser therapy and in most cases trans urethral resection of prostate. These treatment modalities improve the quality of life in most patients but in spite of these treatment modalities some of the patients don't get relief and others feel worse due to side effects of treatment or disease progression. Some of these factors are discussed below.

Genetic and hormonal susceptibility of BPH

A wide variety of genetic factors have been associated with tissue hyperplasia in general Androgen related genes and metabolism genes are closely associated with growth

and function of prostate. The growth of the prostate gland is dependent on circulating androgens and intracellular steroid signaling pathways mediated through the androgen receptor (AR), a ligand-activated nuclear transcription factor. Androgens bind to the AR, stimulating transcription of a cascade of androgen-responsive genes such as prostate-specific antigen (PSA) and genes involved in cell-cycle control. The transactivation of AR that is important for the normal growth and function of the prostate is found in trans activation domain encoded by exon I of the AR gene (Xq11-12) which contains polymorphic CAG and GGC (also GGC) repeats encoding polyglutamine and polyglycine tracts, respectively [4-6].

Male relatives of men with early onset of BPH had a 66% cumulative life time risk of prostatectomy for BPH, compared to a 17% cumulative risk among control relative ($P=0.001$). A 4 fold increase in age specific risk of prostatectomy for BPH was present among relatives of men who had undergone prostatectomy for BPH ($P=0.003$), while brothers of these affected cases had a 6 fold increase in risk ($p=0.0089$) compared to controls. Major risk factor in pathogenesis of BPH. Genetic polymorphism studies of several genes involved in steroid metabolizing pathway has been shown to be associated with increased BPH risk [7,8].

Steroid 5-reductase type II (SRD5A2) is also suggested to be associated with BPH and prostate cancer, but the data are not unequivocal [9]. Transforming growth factor-beta 1 (TGF- β 1) is one of them that plays an important role in the cell cycle regulation and arrests the cell cycle at G1 phase, consequently inhibiting the growth of many kinds of epithelium including prostatic epithelium [10]. Only one study conducted till now that correlated the association of Glu-298-Asp polymorphism of endothelial nitric oxide synthase with BPH [11]. Genetic polymorphism of VDR gene has also been extensively investigated in prostate cancer with substantial co-relation in assessment of risk. Activation of VDR may influence androgen receptor activation leading to the development of BPH and thus polymorphism of VDR has also been investigated in BPH and stated to have risk association [12].

The role of α 1-adrenergic receptors (α 1-adrenoceptors) in BPH has recently been studied. The receptors seem not only increases the tone of prostatic smooth muscle but also modify prostatic growth [13] and contribute to LUTS by affecting the bladder and the spinal cord.

Inflammatory cytokines, molecular studies in BPH

Many studies showed the association between inflammation and development of benign prostatic hyperplasia. Inflammatory infiltrates are frequently observed in prostate tissue specimens from men with BPH and the presence or degree of inflammation has been found to be correlated with prostate volume and weight. The inflammatory injury may contribute to cytokine production by inflammatory cells driving local growth factor production and angiogenesis in the prostatic tissue. This pro inflammatory micro environment is closely related to BPH stromal hyper proliferation and tissue remodeling with a local hypoxia induced by increased oxygen demands by proliferating cells which supports chronic inflammation as a source of oxidative stress leading to tissue injury in infiltrating area. Recent studies strongly suggest that BPH is an immune inflammatory disease. The T-cell activity and

associated autoimmune reaction seem to induce epithelial and stromal cell proliferation.

Other studies suggest the cytokine family of IL-17A, E.F and their receptors are found in BPH. Immuno reactivity for IL-17A, E.F and their receptors IL-17RA, IL-17BR, and IL-17CR, IL-17E and IL-17F was significantly elevated in prostatic tissue from BPH compared with that in controls, which was accompanied by increased numbers of infiltrating inflammatory cells and CD31(+) blood vessels. Their data are compatible with hypothesis that IL-17A acting through IL-17A, but not IL-17CR contribute to the pathogenesis of BPH [16]. Chronic prostatic inflammation (CPI) could be a cause of symptomatic or complicated benign prostatic hyperplasia (BPH). Three proteins (MCP-1/CCL2, IP-10/CXCL10, and MIF) were detected in BPH [14].

One study showed the differential (IHC) expression of CD44s, E-cadherin and β -catenin among hyperplastic and homoplastic lesions of the prostate gland. CD44s had score 3+ in 41.5, 46.7 and 37.8% of areas with NH, HGPIN and PCa, respectively. E-cadherin immunostaining was highly detected in 71.1, 78.5 and 63.0% of NH, HGPIN and PCa areas while β -catenin score 3+ was exclusively membranous in 80.7% of NH and nuclear/cytoplasmic in 70.4 and 48.9% of HGPIN and PCa areas [15].

Another study measured the transcript levels of Aurora kinases and compares them to their immune reactivity patterns in prostate tumors. A total of 26 cases of prostate cancer (PCa) and 38 cases of benign nodular hyperplasia (BPH) were sampled from archived formalin fixed paraffin embedded tissues. Tissue sections were lysed, total RNA extracted and cDNA made by random hexamer priming while slide sections were immunostained for the kinases. Normalized relative quantitation was performed for all the kinases using real-time PCR on TaqMan chemistry. The immune reactivity profile showed 15.4, 53.8 and 30.7% positivity for Aurora kinases A, B and C in PCa cases, respectively, while the positivity was 76.3, 73.7 and 84.2% for the same kinases in BPH cases. The immune reactivity was preponderant on epithelial tissue significantly over expressed in BPH cases compared to PCa cases. At the transcript level, there was no significant differential expression in the kinases between PCa and BPH cases [16].

Anoctamin 1 (ANO1) encodes a Ca (2+)-activated chloride channel (CaCC) that mediates various physiological functions. This study demonstrated that it is essential for testosterone-induced BPH. ANO1 was highly amplified in dihydrotestosterone (DHT) - treated prostate epithelial cells, whereas the selective knock down of ANO1 inhibited DHT-induced cell proliferation and concluded that ANO1 is essential for the development of prostate hyperplasia and is a potential target for the treatment of BPH [17].

Pro-inflammatory cytokines induce inflammatory mediators such as cyclooxygenase -2(COX-2) and inducible nitric oxide (iNOS) that contribute to prostate growth [18]. It is hypothesized that inflammation of the prostate, through the generation of reactive oxygen species (ROS), causes repeated tissue damage and post-translation DNA modifications, thereby inducing neoplasia in the prostate [19]. The major sources of ROS are the mitochondrial respiratory chain, an uncontrolled arachidonic

acid cascade, and NADPH oxidase [20]. These processes make use of molecular oxygen and produce ROS which include superoxide anion and hydrogen peroxide [21]. Elevated ROS production has a deleterious effect and is associated with tissue injury, DNA damage, neoplastic transformation and aberrant growth and proliferation. Thus, disproportionate formation of ROS can result in oxidative stress and might play an important role in the pathogenesis of several prostatic diseases including cancer [22]. Other investigation who have shown that generation of ROS either through the NADPH oxidase system or arachidonic acid pathway lead to the activation of inflammatory signaling pathways, primarily the NF-KB pathway.

Metabolic syndromes (Diabetes, insulin resistance) and BPH

Diabetes significantly increases the risk of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). The major endocrine aberration in connection with the metabolic syndrome is hyperinsulinemia. Insulin is an independent risk factor and a promoter of BPH. Insulin resistance may change the risk of BPH through several biological pathways. Hyperinsulinemia stimulates the liver to produce more insulin-like growth factors (IGF), another mitogen and an anti-apoptotic agent which binds insulin receptor/IGF receptor and stimulates prostate growth. The levels of IGFs and IGF binding proteins (IGFBPs) in prostate tissue and in blood are associated with BPH risk, with the regulation of circulating androgen and growth hormone. Stromal-epithelial interactions play a critical role in the development and growth of the prostate gland and BPH. Previously, we have shown that the expression of C-Jun in the fibroblastic stroma can promote secretion of IGF-I, which stimulates prostate epithelial cell proliferation through activating specific a target gene. Here, we will review the epidemiologic, clinical, and molecular findings which have evaluated the relation between diabetes and development of BPH. Patients with obesity, insulin resistance and androgen deficiency are associated pathological conditions that greatly aggravate the clinical course of LUTS/BPH. Most severe LUTS/BPH was associated with presence of all three mentioned systemic disorders [23].

Obesity, physical activity and lifestyle changes and BPH

Epidemiological and clinical data indicate that modifiable lifestyle factors- including obesity, physical activity, and diet- significantly influence the risks of symptomatic benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). Recent findings: modifiable factors associated with significantly increased risks of symptomatic BPH and LUTS include obesity and consumption of meat and fat. Factors associated with decreased risks include increased physical activity, vegetable consumption, and moderate alcohol intake. Obesity potentially attenuates the clinical efficacy of 5 α -reductase inhibitors (5-ARI). Randomized clinical trials of lifestyle alterations- such as weight loss, exercise, and diet- for the prevention or treatment of BPH and LUTS have yet to be performed. Obesity, physical activity and diet substantially alter the risks of symptomatic BPH and LUTS [24].

5-ARIs exhibit diminished efficacy in obese patients. Although

clinical trials of lifestyle modifications have yet to be undertaken, it is reasonable to promote weight loss, exercise, and healthy diet within the context of standard treatment for symptomatic BPH and LUTS (Benign prostatic hyperplasia, lower urinary tract symptoms and physical activity). This evidence encompasses most established metrics of adiposity, including body mass index, waist circumference and waist-to-hip ratio, and falls under 3 general categories, including prostate volume, clinical benign prostatic hyperplasia and lower urinary tract symptoms. Obesity markedly increases the risk of benign prostatic hyperplasia. Since physical activity decreases the risk of benign prostatic hyperplasia, observations support the development of novel prevention strategies and treatment targeted toward adiposity, weight loss and lifestyle [25].

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Vitamin D and BPH

Increasing intake of vitamin D from diet and supplements has shown a correlation with decreased BPH prevalence. Vitamin D analogues of up to 6000 IU/day have shown to decrease prostate volume in BPH patients. Pre-clinical trials have shown vitamin D to not only decrease BPH cell and prostate cell proliferation alone, but also when induced by known growth promoting molecules such as IL-8, Des (1-3) IGF-1, testosterone and dihydrotestosterone. Among all the studies there have not been any side effects or negative implications with increased vitamin D intake [27].

Serum Zinc and BPH

Zinc is a very important trace element and different studies have shown their association with diarrhea, growth retardation, and different prostatic lesion including BPH. Serum zinc level was studied in different parts of the world with conflicting results. One study in Bangladesh showed gradual progressive increase level of serum zinc in benign, premalignant and malignant lesion of prostate. In BPH the serum zinc level was (mean \pm SD) 10 \pm 26.15, in HGPN 14 \pm 20.95 and prostate cancer 139 \pm 11.09. This gradual increase in zinc level was statistically significant ($p < 0.017$) in other study in India researchers found strong correlation between plasma zinc level and various prostatic diseases. Out of 80 cases studied (20 normal, 50 BPH, 10 cancer). Serum zinc level analysed by atomic absorption photometry the mean zinc level in normal was 94.5 \pm .38, BPH 145.4 \pm 9.67 and 59.6 \pm 3.08 which were highly statistically significant. Another study measured zinc, vitamin A, albumin, copper and retinoid binding protein content in 27 patients with BPH and 19 patients with prostate cancer. A significantly lower zinc level was found in cancer groups ($p < 0.05$) [28].

The study showed that there is gradual progressive increase level of serum zinc found in benign, premalignant and malignant lesion of prostate. In BPH the serum mean \pm SD zinc level was 101 \pm 26.15, in low grade PIN 116 \pm 21.34, high grade PIN 147 \pm 20.95 and in frank prostatic carcinoma it was 139 \pm 11.09 μ m/dl. This

gradual increase in zinc level found in patients having prostatic lesions is statistically significant ($p < 0.017$). Previously two other studies showed the different type of results. In one study in India the researchers found strong correlation between plasma zinc levels and various prostatic diseases. Out of 80 cases studied (20 normal, 50

benign, 10 carcinomatous). Serum zinc level analyzed by atomic absorption spectrophotometry the mean \pm SD plasma zinc level in the normal case was 94.5 ± 10.38 , for benign prostatic lesion it was 145.4 ± 9.67 , 162.4 ± 2.22 , 172 ± 5.27 (78% rise compared to normal patient) in those with fibromuscular prostate, chronic prostatitis and benign prostatic hyperplasia respectively. Patients with malignancy had a plasma zinc level of 59.6 ± 3.08 , (37% fall compared to normal patients). There was highly statistically significant prostatic disease [29,30].

HFD and BPH

The current trend towards an increasingly sedentary lifestyle and increasing consumption of high-caloric 'Western style' high-fat diet (HFD) has contributed to the sharply increasing prevalence of metabolic disorders such as obesity and type 2 diabetes in the United States [46]. Presently, obesity is a major health concern, and according to the Center for Disease Control & Prevention, approximately 40% of the adults in the United States are obese and ~20% of children and adolescents are overweight [31]. A closer examination of obesity has revealed that a preferential accumulation of fat in the abdominal region of men is associated with increased risk of urologic complications including urinary incontinence, erectile dysfunction, benign prostatic hyperplasia (BPH) and perhaps cancer. A strong association between fatty acids and prostate diseases has been reported with several intriguing hypothesis. These including mechanisms involving inflammation, oxidative stress, peroxidation of lipids and accumulation of 8-hydroxy-2'-deoxyguanosine and increased androgen synthesis driving the growth of the prostate. High-fat diet induces a low-grade chronic inflammatory response, a phenomenon designated as 'metabolically triggered inflammation or meta-inflammation. The direct effects of HFD on the prostate are still unclear, though it is considered to cause inflammation and oxidative stress through alteration in various signaling pathways that increase the vulnerability of the prostate to numerous diseases [50]. In this review we focused on the role of HFD in the genesis of oxidative stress and intra prostatic inflammation and their influences on signaling pathways that orchestrate various prostate diseases, including cancer [34].

Surgical and laser treatment of BPH

Transurethral resection of prostate (TURP) still remains the gold standard modality of surgical treatment of obstructive lower urinary tract symptoms due to benign hyperplasia. With meticulous resection and intra operative haemostasis using continuous out flow resectoscope, conventional monopolar TURP is equally safe and effective in large size prostate as compare in small size [35].

Where transurethral resection of prostate (TURP), has been the gold standard surgery for enlarged prostate glands < 80 grams, newer modalities such as laser technology have proliferated with safe and efficacious results. Notably, for prostates larger

than 80-100 grams, the surgical options were and open, simple prostatectomy or perhaps a staged TURP.

Green Light Photo selective vaporization (GL-PVP) with the Green Light XPS 180Watt system deals with bothersome BPH-LUTS with essentially any sized prostate gland, can be treated as same-day surgery requiring no overnight admission to hospital, while continuing necessary anti-coagulants, with significantly diminished risks of bleeding, erectile dysfunction.

The GL-PVP is unique in that there are guides an excellent simulation device (Green Light SIM), and mentoring programs in place. Performing GL-PVP should not be haphazard. A surgical plan based on prostate anatomy and size, cystoscopic appearance, and application of routinized techniques should yield consistent and optimal surgical outcomes. Intra operative and post-operative complications, pre and post operative quality of life (QoL) and international prostate symptoms score (IPSS), operative time, Time to removal of catheter and hospital stay were evaluated between small < 80 gm and large prostate gland > 80 gm volumes. There were quite satisfactory improvement in IPSS and QoL. No significant complications were observed except TUR syndrome in 2 cases from group 2, which were managed well in postoperative period. A comprehensive literature review was performed on laser-assisted prostatectomy between 2006 and 2015. Study presented no significant difference towards the standard treatment (TURP/HoLEP) arm in two randomized controlled trials and favorable outcomes in available prospective cohorts. Observed morbidity was minimum and comparable with the rest of transurethral literature [37]. One study compared the incidence of complications associated with 3 different endoscopic procedures, namely transurethral resection of prostate (TURP), bipolar plasma kinetic resection of the prostate (PKRP), and holmium laser nucleation of prostate (HoLEP) in the treatment of benign prostatic hyperplasia (BPH) and assessed the clinical value of the Clavien-Dindo classification system for standardizing the evaluation of complications. A total of 625 patients with BPH scheduled for endoscopic surgery underwent TURP (214 cases), PKRP (207 cases) or HoLEP (204 cases). The complications were recorded in each group and analyzed using Clavien-Dindo classification system. There were no significant differences in the baseline data among the 3 groups ($p > 0.05$). TURP was associated with higher total incidence rate of complications than PKRP and HoLEP, and the incidences of electrolyte disturbance, massive intra operative hemorrhage, urinary irritation symptom, urinary blockage, transurethral resection syndrome (TRUS), and erectile dysfunction (ED) differed significantly among 3 groups ($P < 0.05$). According to Clavien-Dindo classification, the incidence of grade II complications was significantly higher in TURP group than in PKRP and HoLEP groups ($p < 0.05$), and that of grade III and IV complications was significantly higher in TURP group than in HoLEP group ($p < 0.05$). No significant differences were found in grade I or V complications among 3 groups ($p > 0.05$). They concluded that PKRP and HoLEP are associated with fewer complications with a better safety profile in the treatment of BPH [38].

Different medical treatment modalities for BPH

The first line of treatment of BPH include $\alpha 1$ blockers, 5 α radiates inhibitor. Now a day's silodosin a new uroselective alpha

blocker with high pharmacological selectivity is commonly used. It is effective and well tolerated for treatment in men with LUTS. The therapeutic effect of drug silodosin at a dose of 8mg once daily in patients with symptomatic benign prostatic hyperplasia was assessed in one study. The study reveals the positive dynamics of lower urinary tract symptoms as well as positive changes in the assessment of quality of life. There was statistically significant difference less than 0.001 during first and last visit of medication [39].

Highly selective α 1A-receptor antagonists such as silodosin were developed specifically for the treatment of LUTS because non-selective antagonists were associated with cardiovascular adverse effects. Silodosin is generally well-tolerated and the most common adverse events seen are abnormal ejaculation, dizziness, headache, diarrhea, nasal congestion and orthostatic hypotension. Unlike 5ARIs, α -blockers do not impair libido. Silodosin improves storage/voiding symptoms and nocturia and is effective within the framework of a trial without a catheter. 5 α -reductase inhibitors (5ARIs) are not associated with male breast cancer development. General effect of low-dose tamsulosin (0.2 mg) as a first-line treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia: a systematic review and meta-analysis. That low-dose tamsulosin has generally positive effect and safety in treatment of LUTS and could be a suitable option as an initial treatment, especially for patients with low body mass index, as is typical of Asian people. Dutasteride can be used to improve urinary symptoms (IPSS and Q max) and reduce TPV but with awareness of its potential adverse events. Combination therapy with tamsulosin can be considered when further improvements in symptoms are desired [40]. Another study conducted a multi centered open clinical study on 165 BPH patient and treated them with Saw Palmetto Extract Capsules. The drug was given for 12 weeks. They compared international prostate symptom score (IPSS), prostate volume, post voidal residual volume, urinary flow rate, quality of life score (QOL) and adverse event between the two groups of patients. They compared with baseline, both IPSS and QOL were improved after 6 weeks of medication, and at 12 weeks, significant improvement was found in IPSS, QOL, urinary flow rate and post void residual urine. Mild stomachache occurred in 1 case, which necessitated no treatment. They concluded Saw Palmetto Extract Capsule were safe and effective for the treatment of BPH. One other study evaluated the efficacy and safety of the combination therapy of xipayimaizipizi capsules and tamsulosin in the treatment of benign prostatic hyperplasia (BPH). They randomly assigned BPH patients to a control and combination group of equal number. They treated the patients in the control group with tamsulosin at 0.2 mg qd and those in the combination group with tamsulosin at 0.2 mg qd plus xipayimaizipizi at 0.5 g tid, respectively, both for 4 weeks. Then they obtained the mean frequency of nocturnal urination, maximal urinary flow rate (Qmax), residual urine volume, international prostate symptom score (IPSS), and quality of life score (QOL) of the patients and recorded their adverse reactions. Before treatment the nocturnal urination frequency, Qmax, IPSS and QOL were 3.60 \pm 1.81, (10.40 \pm 3.53) ml/min, 22.47 \pm 8.58 and 4.43 \pm 1.50 in the control group as compared with 3.43 \pm 1.61, (10.14 \pm 3.43) ml/min, 21.93 \pm 8.79 and 4.73 \pm 1.31 in the combination group. After 4 weeks of medication

the combination group showed more significant improvement than the control in the nocturnal urination frequency (1.30 \pm 1.18 vs 2.27 \pm 1.60), Qmax ([13.85 \pm 3.15] vs [14.36 \pm 3.03] ml/min), IPSS (13.00 \pm 1.53 vs 17.20 \pm 8.43), and QOL (2.57 \pm 1.61 vs 2.93 \pm 1.68), all significantly better than the baseline (P < 0.05). The combination therapy achieved remarkable improvement as compared with the control in the nocturnal urinary frequency (-[2.17 \pm 1.12] vs-[1.50 \pm 1.01]) (p < 0.05), but exhibited no significant differences from the latter in Qmax ([3.72 \pm 2.281] vs [3.95 \pm 2.53] ml/min) and residual urine volume (-[34.30 \pm 37.43] vs-[26.43 \pm 30.49] ml) (p > 0.05). Adverse reactions were found in 5 case in the combination group (16.67%) and 3 cases in the control (10%) with no remarkable differences between the two groups (p > 0.005). They concluded the combination therapy of xipayimaizipizi capsules and tamsulosin can improve the symptoms of BPH and the patient's quality of life [41]. Yet another study reviewed the clinical studies on combination therapy of 5 α reductase inhibitors and α 1 blockers in patients with BPH. These data demonstrate a significant advantage of combination therapy versus monotherapy in terms of quality of life and subjective symptoms as well as the safety, better results in the prevention of BPH progression and acute urinary retention and reduced need for surgery [42]. The use of fixed combination therapy would involve an increase in persistence due to the lower rate of patients abandoning treatment overtime. Each 30 day increment of 5 ARI therapies, i.e. for an expenditure of 10.6 million euro's extra per year for 5 ARI medications, savings of approximately 24.3 million euro's in hospital costs could be achieved. 1-Blockers are the most frequently prescribed oral medications as first line treatment. They evaluated QoL and sexuality in patients requiring treatment by Alfuzosin 10 mg once daily according to physician decision in current practice and identified patients profile conditions by Tunisian urologists. The treatment compliance to Alfuzosin was very good with a regular intake in 92% of the cases. Quality of life significantly improves during visits: the global IPSS score decreases from 18.8 at baseline to 9.5 at 6 months. The same favorable volition was observed with the bother score which decreases from 4.0 at baseline to 1.6 at 6 months, and with MSHQ-EJD score which increases from 10.5 at first visit to 11.4 at 6 months. They concluded that alfuzosin 10 mg administered for 6 months provides a marked improvement in patients presenting symptomatic BPH not only on LUTS but also in QoL and sexual disorder. The literature is still very limited. Based on the available data, the approach is safe and effective, demonstrating favorable outcomes, comparable with the current standard treatment options. Further documentation of THULEP outcomes is necessary to define the optimum indications of this novel technique [44].

BPH & prostatic cancer

BPH is one of the most common diseases of older men, with more than 70% of men over 70 years affected, and prostate cancer is the most common cancer in men in the UK. Prostate cancer generally presents in one of three ways: asymptomatic patients who are screened (usually by a PSA test); men with LUTS who are investigated and undergo prostate biopsy; or patients with symptoms of metastasis such as bone pain. Men can be reassured that the main cause of LUTS is BPH. Only a small proportion of men have LUTS that are directly attributable to

prostate cancer. Digital rectal examination gives an evaluation of prostate size, which is relevant in particular to BPH management, and along with PSA testing it is one of the only ways of differentiating clinically between BPH and prostate cancer. If a nodular abnormality is present there is around a 50% chance of a diagnosis of prostate cancer being made on biopsy. Raised levels of serum PSA may be suggestive of prostate cancer, but diagnosis requires histological confirmation in almost every case. A normal PSA, PSA density and DRE can give reasonable confidence with regards to excluding clinically significant prostate cancer. BPH is not a known risk factor for prostate cancer, although the two frequently coexist. Age is the strongest predictor of prostate cancer risk, along with family history. BPH is not considered to be a precursor of prostate cancer. It is likely that although BPH is not considered to be a precursor of prostate cancer. It is likely that although BPH may not make prostate cancer more likely to occur, it may increase the chance of diagnosis and incidental cancer [45].

DISCUSSION AND CONCLUSION

Review of literature and accumulated evidence suggests that genetic polymorphism, hormonal dysregulation, different inflammatory cytokines, Vitamin D, metabolic syndromes Trace element zinc is also implicated in BPH. Transcription factors and high fat diet plays a significant role in the development of BPH. Though the precise molecular mechanisms potentiating prostate growth mediated by these factors are unclear, current literature review and different research work done supports this. Although TURP is the gold standard treatment for BPH, still combination of other type of surgery like PKRP and HoLEP are associated with fewer complications and a better safety profile in treatment of BPH. Although alpha & and β adrenergic drugs are effective first line treatment for BPH still combined multiple drug also helps reducing BPH associated symptoms more effectively. In summary literature on already performed research demonstrated that use of multi drug, combined surgery, zinc, vitamin D, metabolic syndromes and fiber rich diet can provide an opportunity for better quality of life, relief of symptom associated with BPH and help in reducing cost and morbidity in BPH patients. Genetic, hormonal factors, inflammatory cytokines, molecular level changes, Zinc, Vitamin D HDF are responsible for neoplastic proliferation of prostate leading to BPH. These provide avenues for further research in defining preventive strategies for BPH.

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