Drug Corner

# Association between Benign Prostatic Hyperplasia and Metabolic Syndrome : A Clinical Update

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**The prevalence of metabolic Syndrome (MetS) in men with benign prostatic hyperplasia (BPH) as reported by Asian Studies was 26.7% to 55.4%, Men with MetS have higher prostate volume and higher prostate growth rate. Insulin resistance, increased visceral adiposity, low androgen high estrogen levels, low grade inflammatory state, dyslipidemia are all contributory factors. The treatment options include lifestyle modification, alpha 1 adrenoreceptor blocker, 5 alpha reductase inhibitors, PDE5 inhibitors. Combination of 5 α reductase inhibitors and α-blockers provides relief to LUTS and prevents progression of BPH.**

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***Key words*** **: Metabolic Syndrome, BPH, Combination therapy.**

In benign prostatic hyperplasia (BPH), there is an enlargement of the prostate gland characterized by the formation of hyperplasic nodules in prostate, and related lower urinary tract symptoms (LUTS).[1,2] It is highly prevalent among middle-aged and elderly men. The only two principal determinants known earlier which increases the BPH risk were aging and androgens. But, recent evidence suggest that there are number of modifiable risk factors such as obesity which have an important role in the development of BPH.[2] An association was observed between BPH and metabolic syndrome (MetS), or its components.[3]

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*Metabolic syndrome is a complex disorders related to metabolic abnormalities*such as obesity, hypertension, dyslipidemia, insulin-resistance with compensatory hyperinsulinemia, and glucose intolerance.[2] *These metabolic abnormalities can lead to development of BPH and lower urinary tract symptoms (LUTS) in men.*[1]

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As per the recent study, *men with MetS have higher total prostate volume*, by difference of 1.8-10.2 mL and *significantly higher prostate growth rate*than those without MS.[1,4] The number of MetScomponents an individual possess is positively associated with risk of BPH. Also, men with BPH have substantially greater odds of having metabolic syndrome. In the same way, men present with MetScould also be assessed for LUTS/BPH, this would help to improve quality of life and also to identify men at risk of BPH progression.[3]

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***Editor's Comment :***

- **An association has been found between benign prostatic hyperplasia and metabolic syndrome.**
- **Three hit mechanism of prostatic inflammation, metabolic changes and altered sex steroid levels lead to prostatic hyperplasia.**
- **Therapy should involve lifestyle changes, α-blockers, 5α reductase inhibitors and PDE 5 inhibitors for BPH and LUTS.**

## Pathophysiology of MetS and BPH :

Though epidemiological data suggests the link between MetS and BPH/LUTS but, the exact biological pathways are still unclear. Several key factors have been identified and postulated to be responsible in such pathophysiological processes are listed below.[1]

**(a) Insulin resistance :**

Insulin is a growth factor for prostatic epithelial cells. Directly or indirectly hyperinsulinaemiathrough obesity and its altered hormone metabolism can increase genestranscription involved in sex hormone metabolism. It increasesthe risk of BPH by increasing the amount of androgen and estrogen entering prostatic cells. Also, insulin-like growth factor 1 (IGF-1) promote prostate epithelial growth and associated with BPHrisk. Due to homology of insulin receptor with IGF receptor, *insulin can bind to IGF receptor and activate the IGF signaling pathway to promote the prostatic growth.*

**(b) Increased visceral adiposity :**

Obesity increases the aromatase activity which further increases estradiol production which inhibits gonadotropin secretion and the production of

testosterone. This hypogonadal obesity cycle results in an increased estrogen to androgen ratio leads to hypogonadal state. *Each kg/m$^2$ increase in BMI leads to 0.41 mL increase in prostate volume.* As compared to non-obese patients, obese patients had a 3.5-fold increasedrisk of an enlarged prostate.One of the study have reported that obesity increases the BPH risk by 28%.

**(c) Sex steroid :**

Like MetS, low androgen and high estrogen levels were also observed in menwith LUTS and BPH. The smooth muscle hyperplasia increased with lowdihydrotestosterone (DHT) level in the transition zone of the prostate. Hyperinsulinaemiacan indirectly cause BPH by its effect on obesity and sex hormones. This *sex hormones can increases the BPH risk by activating DNA synthesis and cellular proliferation due to their androgenic actions in the prostate*.

**(d) Dyslipidaemia :**

In BPH patients, low level of HDL-C and high levels of total cholesterol and low density lipoprotein cholesterol (LDL-C) were observed than in controls. While, one study reported no significant association between total cholesterol, HDL-C, triglycerides, triglyceride to HDL-C ratio and the risk of BPH.

**(e) Chronic low grade pro-inflammatory state:**

The chronic low grade inflammation, with elevated levels of inflammation markers for instance, C-reactive protein (CRP), pro inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-8, IL-6, and IL-1 was associated with MetS. In prostate inflammatory infiltrates, the T-cell activities can result in stimulation of stromal and epithelial cell proliferation that is sustained by an autoimmune mechanism. Chronic inflammation induced tissue damages and consequent chronic process of repetitive wound healing may lead to the development of BPH nodules.

**(f) Three-hit mechanism :**

A three-hit hypothesis has been proposed by Vignozzi *et al* on the pathogenesis of BPH under metabolic influence. An induced prostatic inflammation (first hit) can be auto sustained or overlapped by metabolic changes (second hit) and sex steroid aberrations (third hit). The combined actions of two or three hits result in overexpression of Toll-like receptors, transformation of prostatic cells into antigen-presenting cells, activation of resident human prostate-associated lymphoid tissue and over production of growth factors thus, contributes to the prostate remodeling and enlargement.[1]

**Overlapping symptoms of BPH :**

As reported, LUTS has multiple causes, it is important to understand that LUTS in men maynot be caused by the prostate.There is an overlap of both obstructive voiding symptoms and storage symptoms for most men with LUTS (Fig 1). Certainly, it isthe storage symptoms but, not the voiding symptoms which is associated with prostate enlargement. In men with BPH, they are the most troublesome group of LUTS.[5]

Since, the symptoms of OAB and LUTS secondary to BPH overlap, it is possible that LUTS in most of the men who suffer from this condition may be due tothe bladder dysfunction.[6]

For the patients with bothersome voiding and storage LUTS at low risk of progression, the standard pharmacologic treatment should be a α1-Adrenoreceptor (α1-AR) antagonist.While, the combination alpha blocker (α1-AR antagonist) plus anti-muscarinic agent is an appropriate and valid treatment option for patients with voiding and persistent storage symptoms, providing their post-voiding residual is ≤200 mL.[5]

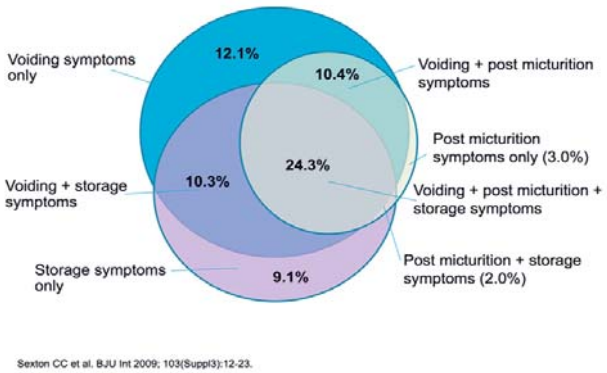
**Treatment Options of MetS-Associated BPH/LUTS:**

Multiple new treatment modalities for symptomatic BPH have arisen over the last decade. The treatment options-ranges from watchful waiting to open surgery. This range is as broad as the BPH spectrum of symptoms. The aim of BPH therapy is to improve quality of life by providing symptom relief and increasing maximum flow rate as well as reducing disease progression and the development of new morbidities.[7]

Current therapy for BPH/LUTS is largely based on the use of á-adrenergic receptor blockers, and 5-$\alpha_1$ reductase inhibitors. Current EAU guidelines recommends $\alpha_1$-blockers and 5-α reductase inhibitors for the treatment of men with moderate-to-severe LUTS. It also suggest the usefulness of lifestyle modifications.[8]

## ■ Lifestyle Modifications

Lifestyle intervention emerges as a novel opportunity for the prevention and treatment of BPH.[1]The type of diet and level of physical activity affect the prostate




Sexton CC et al. BJU Int 2009; 103(Suppl3):12-23.

Fig 1 — Most men have both voiding and storage symptoms.[5]

health in the aging male, most probably reducing risk factors such as MetS, hypogonadism, and inflammation. Some of the evidence have suggested that high consumption of red meat and a high fat diet increased the BPH risk. Also, high vegetables consumption reduces the risk of BPH.Physical activity reduces the risk of prostate enlargement, LUTS, and LUTS-related surgery. Increasing walking by 3 h/week decreases the risk of BPHby 10%.[8] While, moderate to vigorous physical activity can reduce BPH risk up to 25% as compared to a sedentary lifestyle.[1]

### ■ Watchful Waiting

It is a management strategy in which the patient is monitored by the physician without receiving any active intervention.

### ■ Alpha one adrenoreceptor blockers ($\alpha_1$- AR blockers)

It is the first line treatment option for the symptomatic relief of BPH. Presently, $\alpha_1$-adrenoreceptor antagonists are common for treating BPH related LUTS. They relax the smooth muscle of the prostate by blocking $\alpha_1$-receptor mediated sympathetic stimulation.Currently available $\alpha_1$-blockers arenonselective $\alpha_1$-blockers, terazosin, doxazosin, and alfuzosin, and the highly selective $\alpha$1A-blocker, tamsulosin. They are well-tolerated drug class but, cardiovascular side-effects can occur and can lead to serious morbidity such as falls and fractures. While, the safety of tamsulosinis better documented than other $\alpha_1$-AR antagonists in such risk groups in LUTS/BPH patients.

### ■ 5-alpha reductase inhibitors (5ARIs)

It inhibit the conversion of testosterone to DHT which is the primary androgen involved in both normal and abnormal prostate growth. Currently available 5 ARIs for the management of BPH arefinasteride and dutasteride. The only available 5 ARIs which inhibit both type 1 and type II 5 $\alpha$-reductase is Dutasteride which induces a more profound reduction of serum DHT in the range of 90–95% compared with 70-75% for finasteride.[7]

### ■ PDE-5 Inhibitors (PDE5i)

PDE5i reduce moderate-to-severe LUTS in men with or without ED. Accordingly, tadalafil (5mg once daily) has been approved by the US Food and Drug Administration and the European Medical Agency (EMA) for the treatment of male LUTS in Europe.[8]

### ■ Combination therapies

Most of the guidelines suggested the combination of 5-áreductase inhibitors or and $\alpha$-blockers as appropriate treatment for patients with LUTS with demonstrated prostatic enlargement. The combination has the potential to address the concern associated with mono therapy. Also, the 4-yr CombAT data suggest the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement.[7]

The Combination therapy provide relief from symptoms and also reduces the risk of BPH progression, it means increase of the symptom score, surgical treatment due urinary retention, urinary incontinence, urinary tract infection and renal failure.[9]

### ■ Minimally invasive therapies

In minimally invasive therapies (MITs) the prostate gland is heated by various means (electrical, microwave, laser). Insertion can be directly into the prostate via a needle or into the urethra via a catheter, probe or endoscope.[7]

### ■ Phytotherapy

One of the several phytotherapeutic agents available for the treatment of BPH is Cernilton which is prepared from the rye-grass pollen Secalecereale. It is used worldwide by millions of men and is a registered pharmaceutical product. Evidences suggests that Cernilton is well tolerated and improves overall urological symptoms, including nocturia.[7]

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