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Hypothesis

# A cyclooxygenase-2 inhibitor reduces serum prostatic-specific antigen levels in men with benign prostatic hyperplasia and lower urinary tract symptoms and helps differentiate chronic inflammation from prostate cancer

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ABSTRACT

Emerging evidence indicates that prostatic inflammation may contribute to prostatic growth in benign prostatic hyperplasia (BPH) and neoplastic changes (prostate cancer). The Medical Therapy of Prostatic Symptoms study showed that men with inflammation had a significantly higher risk of BPH progression and acute urinary retention. Evidence also shows that a cyclooxygenase-2 (COX-2) inhibitor can increase apoptotic activity in human BPH tissue. COX-2 inhibitors in combination with alpha-adrenergic blockers may increase the effectiveness of therapy for lower urinary tract symptoms (LUTS) secondary to BPH without significant side effects. COX-2 inhibitors may decrease the serum prostatic-specific antigen level and act as a biomarker to differentiate chronic inflammation from prostate cancer in patients with LUTS suggestive of BPH who do not have a palpable prostate nodule but have a serum prostatic-specific antigen level higher than 4 ng/mL. The results might provide a simple way to initially differentiate chronic inflammation from prostatic cancer. If chronic inflammation of the prostate can be reduced by COX-2 inhibitor treatment, bothersome LUTS as well as voiding conditions might be improved.



## 1. Lower urinary tract symptoms and inflammation

Lower urinary tract symptoms (LUTS) are commonly divided into storage, voiding, and postmicturition symptoms. Male LUTS are historically linked to benign prostatic hyperplasia (BPH) but are not necessarily prostate related. Women and children may also have LUTS. LUTS include symptoms of overactive bladder (OAB), which are often associated with detrusor overactivity and increased bladder sensation. Recent studies revealed that chronic inflammation of the urinary tract could be an etiology for LUTS in men and women. Elevated levels of urinary nerve growth factor as well as C-reactive protein have been reported in patients with OAB and in men with BPH [1,2].

Treatment for male LUTS/BPH has traditionally involved the use of alpha-1 adrenoceptor antagonists (alpha-blockers) and 5-alpha-reductase inhibitors with satisfactory results. However, some patients still do not benefit from these treatments. Adding anti-muscarinic agents has been shown to have beneficial effects on LUTS/BPH refractory to alpha-blocker therapy [3]. Bladder dysfunction is likely to be the cause of symptoms in this subgroup of patients [4].

A retrospective study reviewing all histopathological examinations of BPH in patients undergoing transurethral resection of the prostate showed that chronic inflammation was present in 43.1% of prostate specimens. Chronic inflammation was noted in association with BPH in 43.1% of cases. There was a significant trend to increase with age decades for high-grade prostatic intraepithelial neoplasia. A significant difference was found in incidental prostate carcinoma (IC, T1a, and T1b) distribution in the different decades of age; and especially in regards to both T1a and T1b tumors, there was a trend to increase with patient age. Different histological variables associated to BPH are differently influenced by the age of patients and prostate volume, and they differently influence serum prostatic-specific antigen (PSA) levels [5].

## 2. Cyclooxygenase-2 inhibitor effects on LUTS and prostate disease

Emerging evidence indicates that prostatic inflammation may contribute to prostatic growth in BPH and neoplastic changes (prostate cancer). The Medical Therapy of Prostatic Symptoms

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study showed that men with inflammation had a significantly higher risk of BPH progression and acute urinary retention [6]. Evidence also shows that a cyclooxygenase-2 (COX-2) inhibitor can increase apoptotic activity in human BPH tissue. Analyses of bacterial colonization in prostate cancer and normal prostate tissue showed a highly suggestive correlation between bacterial colonization/chronic inflammation and the diagnosis of prostate cancer [7]. Evidence from genetic studies supports the hypothesis that prostate inflammation may be a cause of prostate cancer development. Proliferative inflammatory atrophy has been considered as an early histologic precursor to prostatic intraepithelial neoplasia and prostate cancer. The concept that inflammation can promote chronic prostatic diseases, such as BPH or prostate cancer, is actually supported by several new significant findings [8].

COX-2 is expressed in human BPH tissue and displays either a proinflammatory effect or a proliferative effect on prostate cells. In a single-center unblinded trial, 46 consecutive men with LUTS and BPH were randomized to receive rofecoxib 25 mg/d plus finasteride 5 mg/d (Group B) versus finasteride 5 mg/d alone (Group A) for 24 weeks. The advantages of the combination therapy compared with finasteride alone were significant after a short time (4 weeks). It can be hypothesized that the association of rofecoxib with finasteride induces a more rapid improvement in clinical results until the effect of finasteride becomes predominant [9].

Fifty-seven patients complaining of LUTS secondary to BPH were randomly assigned to receive doxazosin 4 mg or doxazosin 4 mg plus tenoxicam 20 mg. The total International Prostate Symptom Score, International Prostate Symptom Score quality-of-life index, and Overactive Bladder Symptom Score decreased significantly in both groups compared with baseline ($p < 0.01$). The improvements in these parameters were significantly better in patients treated with combination therapy ($p < 0.05$) [10]. COX-2 inhibitors in combination with alpha-blockers may increase the effectiveness of therapy for LUTS secondary to BPH without significant side effects.

Nocturia is a well-recognized symptom of BPH and is commonly treated by alpha-blockers and/or 5-alpha-reductase inhibitors. However, the effectiveness of these drugs for nocturia has been reported to be only 25%–39%. Intravesical instillation with COX-2 inhibitors can reduce cyclophosphamide-induced bladder hyperactivity and expression of inducible notric oxide synthase and nerve growth factor. Intravesical instillation with COX-2 inhibitors can be considered a possible treatment for OAB [11]. One recent clinical study investigated the efficacy of celecoxib, a COX-2 inhibitor, in the treatment of patients with BPH complaining of nocturia. The results showed that celecoxib is effective in the treatment of patients with BPH complaining of refractory nocturia and suggested that this is a novel treatment option for this common condition [12].

## 3. COX-2 inhibitor effects on PSA and prostatic disease

PSA is a sensitive biomarker for prostate cancer. However, serum PSA level also increase in patients with large BPH and acute and chronic prostatitis. Urologists usually recommend a prostatic biopsy for patients with an elevated serum PSA. The positive biopsy rate was 22% and 10% for the first and repeat biopsy in patients with suspected prostate cancer. Immediate morbidity included rectal bleeding (2.1%), mild hematuria (62%), severe hematuria (0.7%), and moderate-to-severe vasovagal episodes (2.8%). Delayed morbidity comprised fever (2.9%), hematospermia (9.8%), recurrent mild hematuria (15.9%), persistent dysuria (7.2%), and urinary tract infection (10.9%) [13]. If we can use pharmacological manipulation and adequately treat chronic inflammation in patients with LUTS/BPH and elevated PSA levels, prostatic biopsy could be avoided in some patients and the complication rate might be reduced.

## 4. Hypothesis

Chronic inflammation has been considered a possible but important factor inducing LUTS and promoting prostatic growth. PSA elevation is a sensitive but not specific sign of prostatic cancer. To reduce the need for prostatic biopsy in patients with an elevated serum PSA level, it is mandatory to find a simple method for initial differentiation of chronic inflammation from prostatic cancer. We hypothesize that COX-2 inhibitors might decrease serum PSA levels and act as a tool to differentiate chronic inflammation from prostate cancer in patients with LUTS/BPH who do not have a palpable prostate nodule but have a serum PSA level higher than 4 ng/mL.

If serum PSA can be reduced significantly after celecoxib therapy and the positive rate following prostatic biopsy is lower than that in patients without a reduced PSA after celecoxib treatment, we might use COX-2 inhibitor treatment for the initial management of an elevated PSA level in men with LUTS/BPH who do not have a palpable nodule. Furthermore, if chronic inflammation of the prostate can be reduced, bothersome LUTS and voiding conditions might be improved. This can be another benefit for men with LUTS who are worried about surgical intervention.

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