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Original article

Asymptomatic prostatic inflammation in men with clinical BPH and erectile dysfunction affects the positive predictive value of prostate-specific antigen

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Abstract

Objective: To test the hypothesis that sexual dysfunction in elderly men with benign prostatic hyperplasia leads to prostatic inflammation, diagnosed by prostatic fluid interleukin-8 (IL-8), which lowers the positive predictive value of prostate-specific antigen (PSA).

Methods: Overall, 160 men with lower urinary tract symptoms between 50 and 75 years of age with an elevated PSA level of more than 4 ng/ml with normal digital rectal examination and 50 age-matched controls with normal PSA level were prospectively evaluated for prostatic fluid IL-8 levels. Erectile dysfunction was measured by self-administered questionnaire of the Sexual Health Inventory for Men. Total and free serum PSA levels and IL-8 in prostatic fluid were measured 6 to 8 weeks after a course of 400 mg of ofloxacin and 20 mg of piroxicam given daily for 2 weeks. Transrectal ultrasonography–guided biopsy was done only when PSA level did not decrease less than 4 ng/ml.

Results: Mean ages of patients and controls were 63.18 (standard deviation [SD] ± 7.10) and 60.18 (SD + 6.02) years, respectively. Mean concentration of IL-8 in prostatic fluid of the patients was significantly higher, i.e., 6678 pg/ml (SD ± 1985.7) than in control, i.e., 1543 pg/ml (SD ± 375.7) ($P < 0.001$). Following anti-inflammatory treatment, there was a significant decrease in the mean level of IL-8 from baseline to 5622 pg/ml (SD ± 1870.66) ($P < 0.001$). Corresponding to this, a significant decrease was noted in total PSA levels to less than 4 ng/ml in 105 (65.62%) patients. Men with the highest levels of IL-8 had a greater degree of erectile dysfunction.

Conclusion: Men with symptomatic benign prostatic hyperplasia and erectile dysfunction had significant inflammation of the prostate to cause spurious rise in PSA level resulting in an unnecessary biopsy.

Keywords: Prostate-specific antigen; Benign prostate hyperplasia; Asymptomatic prostatitis

1. Introduction

Several convincing studies have shown that men with lower urinary tract symptoms (LUTS) have the same risk of prostate cancer as asymptomatic men of the same age [1–3]. However, men with LUTS do have an increased risk of unnecessary biopsy if the threshold is taken same as in asymptomatic men [1–3].

Prostatitis is a diagnosis of young men, but inflammation in the prostate is also documented in elderly men presenting with LUTS. Patients presenting with clinical benign prostatic hyperplasia (BPH) may have a component of category IV, asymptomatic prostatitis [4–6]. There is evidence in the literature that chronic asymptomatic prostatitis causes elevation in prostate-specific antigen (PSA), and 2 weeks of antibiotic treatment results in significant reduction in PSA [7–9]. The most accurate marker to assess inflammation in prostate is interleukin-8 (IL-8), which is assessed in prostatic expressate [10,11]. The objectives of this study were to test the hypothesis that the lower positive predictive value of PSA to diagnose

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prostate cancer is owing to the presence of inflammation in the prostate, and inflammation, in turn, is associated with erectile dysfunction (ED).

2. Methods

Design of the study was prospective nonrandomized interventional trial. A permission from institute ethical committee (A-02: PGI/EMP/IEC/45/7-2-2009) was obtained. From June 2009 to September 2010, men presenting with LUTS owing to benign prostate hyperplasia, between the ages of 50 and 75 years, who had an elevated PSA of more than 4 ng/ml and normal digital rectal examination (DRE), were included in the study. A repeat total and free PSA level examination was done at the time of recruitment.

3. Study plan

All the patients provided informed consent, and clinical data were captured pertaining to the patients' initial symptoms as AUA symptom score, personal habits, sexual history, and other comorbidities. ED was measured by self-administered questionnaire of the Sexual Health Inventory for Men score containing 5 domains of sexual function. Men were grouped as having no ED, scores 22 to 25; mild ED, scores, 17 to 21; mild to moderate ED, scores 12 to 16; moderate ED, scores 8 to 11; and severe ED, scores 5 to 7.

Prostatic fluid was collected for measuring the levels of IL-8 after doing prostatic massage (by a finger passed rectally and pressing on prostate in one direction from lateral to medial and from above to downward for 2 min).

Patients with elevated PSA levels were given 2 weeks of antibiotics and anti-inflammatory drugs (400 mg of ofloxacin daily and 20 mg of piroxicam daily after meal). Repeat total and free PSA level examination was done in the subjects only after 6 weeks of starting treatment. When a repeat total PSA was more than 4 ng/ml, then only the transrectal ultrasonography (TRUS)-guided biopsy was performed by taking 10 to 12 cores. Patients who showed decrease in PSA level to less than 4 ng/ml were followed up every 3 months with total PSA level examination.

3.1. Exclusion criteria

Patients who had positive urine culture results, history of sexual encounter, masturbation within 5 days, acute and chronic bacterial prostatitis, painful ejaculation, pain in the penis or perineum (category III prostatitis) were excluded. Patients who were on 5α-reductase inhibitors, had history of retention or history of antibiotics and anti-inflammatory for some other causes, prostate biopsy or transurethral resection of the prostate were also excluded.

3.2. Measurement of total and free serum PSA level by enzyme-linked immunosorbent assay

Total and free serum PSA levels were measured by an immunoenzymetric assay kit (DSI PSA EIA, Italy) that have minimum detectable value <0.001 ng/ml from single laboratory of the department of urology. Total and free PSA levels were measured in 160 patients before and after the treatment.

3.3. Controls

A total of 50 men between 50 and 70 years of age with no LUTS (no clinical BPH) with normal DRE and PSA levels were taken as controls. Prostatic fluid was obtained in the similar way as in cases for measuring IL-8.

3.4. Measurement of prostatic fluid IL-8 level by enzyme-linked immunosorbent assay

Prostatic fluid volume was recorded, and samples were centrifuged at 2000*g* for 15 minutes and then were aliquoted and stored at -70°C until further use. Prostatic fluid levels of IL-8 were measured by immunoenzymetric assay kit (IL-8 ELISA kit, Pierce) before and after treatment in patients.

3.5. Statistical analysis

Statistical analysis was done on SPSS 15.0. Paired t test was used to compare means. A 2-tailed $P < 0.05$ was considered significant. Pearson correlation test was applied to correlate the levels of IL-8 with the Sexual Health Inventory for Men score.

4. Results

Mean ages of patients and controls were 63.18 (standard deviation [SD] $\pm$ 7.10) and 60.18 (SD $\pm$ 6.02) years, respectively. Mean value of total serum PSA level of patients at the time of presentation was 7.0 ng/ml (SD $\pm$ 5.12) and of controls was 0.88 ng/ml (SD $\pm$ 0.84). Of 160 patients, 105 (65.62%) showed reduction in PSA level less than 4.0 ng/ml. Decrease in the pretreatment levels of PSA was observed (but still >4.0 ng/ml) in 45 patients and 10 patients showed elevation from the pretreatment levels of PSA. Of 55 patients who did not show reduction in PSA values less 4 ng/ml after the treatment, only 47 had TRUS-guided biopsy (Fig. 1). Of the 47 patients, 25 were detected to have adenocarcinoma of the prostate, whereas 22 patients showed no evidence of malignancy and were followed up with examination of PSA level. At the mean follow-up of 24 $\pm$ 5 months, 93 of 160 patients (58%) continued to have normal PSA levels results. Among 22 patients who had BPH on histopathology, only 9 patients had an increase in PSA levels. The number of men undergoing second biopsy was very low, therefore it was not analyzed.