Chronic Prostate Inflammation Predicts Symptom Progression in Patients with Chronic Prostatitis/Chronic Pelvic Pain

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Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

CP/CPPS = chronic prostatitis/chronic pelvic pain syndrome

CPSI = Chronic Prostatitis Symptom Index

I-PSS = International Prostate Symptom Score

PSA = prostate specific antigen

PV = prostate volume

PVR = post-void residual urine volume

REDUCE = REduction by DUtasteride of prostate Cancer Events

Purpose: We examined the 4-year longitudinal association between histological prostate inflammation and chronic prostatitis/chronic pelvic pain syndrome. We also studied the development of new and progressing existing chronic prostatitis/chronic pelvic pain syndrome in men randomized to placebo in the REDUCE (REduction by DUtasteride of prostate Cancer Events) population.

Materials and Methods: At multiple time points during 4 years univariable and multivariable analyses were performed between acute and chronic inflammation detected on baseline biopsies and the incidence of chronic pelvic pain syndrome-like symptoms, defined as a positive response to CPSI (Chronic Prostatitis Symptom Index) question 1a—perineal pain and/or question 2b—ejaculatory pain and a total pain subscore of at least 4, and progression of chronic prostatitis/chronic pelvic pain syndrome, defined as a 4-point or greater increase from baseline in total CPSI score, in patients with a baseline categorization of chronic prostatitis/chronic pelvic pain syndrome.

Results: Of the 4,109 men in the study acute and chronic inflammation was detected in 641 (15.6%) and 3,216 (78.3%), respectively. Chronic prostatitis/chronic pelvic pain syndrome symptom status was available for 2,816 at baseline. Chronic prostatitis/chronic pelvic pain syndrome-like symptoms developed in 317 of 2,150 men without the condition at baseline who had followup data. Acute and chronic inflammation was not associated with the incidence of the symptoms ($p > 0.1$). At a median followup of 12.0 months 109 of 145 men with baseline chronic prostatitis/chronic pelvic pain syndrome and followup data showed symptomatic progression. Chronic but not acute inflammation was significantly associated with shorter time to progression on univariable and multivariable analyses ($p = 0.029$ and 0.018, respectively).

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Conclusions: Inflammation is not associated with an increased risk of chronic prostatitis/chronic pelvic pain syndrome. However, chronic inflammation predicts the risk of symptomatic progression in men in whom chronic prostatitis/chronic pelvic pain syndrome symptoms have been identified.

Key Words: prostate, prostatitis, pelvic pain, inflammation, chronic pain

THE clinical diagnosis of prostatitis has traditionally been linked to prostate infection and inflammation. In the last half century we came to realize that the majority of men diagnosed with prostatitis do not have active infection and they were referred to as having nonbacterial or abacterial prostatitis. However, the symptoms experienced by these men were still believed to be due to prostate inflammation. These patients are now classified as having CP/CPPS category III.[1] They can be even further categorized as those with demonstrable inflammation in prostate specimen urine and prostatic fluid specimens (category IIIA) and those with no demonstrable inflammation in these specimens (category IIIB). To further complicate things, we now understand that men may have prostate inflammation but remain asymptomatic (category IV).

Research to date has shown a relative disconnection between prostate inflammation and CP/CPPS. Studies have indicated no apparent association of inflammation in EPS/VB3 (expressed prostatic secretion/voided bladder 3) with symptom severity,[2] histological inflammation, or CP/CPPS diagnosis[3] or symptoms.[4] Furthermore, there appears to be no clinically significant difference between inflammation in men with CP/CPPS and asymptomatic controls,[5] and no differential treatment benefits of inflammation stratification.[6,7]

We do not know the relevance of histological inflammation and its relationship to CP/CPPS symptoms. Does evidence of inflammation in the prostate predict CP/CPPS outcomes, prevalence (symptoms), incidence (development of symptoms), severity (symptoms) and/or progression (increase in symptoms)?

We previously reported a cross-sectional examination of baseline data on all patients enrolled in the REDUCE trial, a 4-year, phase 3, placebo controlled study to determine whether daily dutasteride 0.5 mg reduces the risk of biopsy detectable prostate cancer.[8] That study failed to show any significant relationship between the presence of prostate inflammation and CP/CPPS-like symptoms.[4] Entrance criteria for REDUCE included a prostate cancer negative biopsy prior to enrollment with a priori evaluation of the inflammatory status of the tissue.[8]

In the current study we examined the 4-year longitudinal association between CP/CPPS-like symptoms, the development of new CP/CPPS, the progression of existing CP/CPPS and histological prostate inflammation in the men randomized to placebo in the REDUCE population.

METHODS

The design of REDUCE was described previously.[8] Briefly, eligible men were 50 to 75 years old and had serum PSA 2.5 or greater, or 3.0 ng/ml according to age (50 to 60 or older than 60 to 75 years, respectively) but 10 ng/ml or less and a single negative prostate biopsy (6 to 12 cores) within 6 months of enrollment. Men were excluded from study if they had a history of prostate cancer, high grade intraepithelial neoplasia, atypical small acinar proliferation or PV greater than 80 cm^3, underwent previous prostate surgery or had I-PSS 25 or greater, or 20 or greater on α-blockers.

At the screening and randomization visits data on demographics, medical history, physical examination, PV measured by ultrasonography, PSA, I-PSS, quality of life, peak urinary flow and PVR were collected. Participants were randomized in double-blind fashion to receive oral dutasteride 0.5 mg or placebo daily and they were followed every 6 months for 4 years.

Baseline biopsies had been performed before the start of the study and were reread centrally elsewhere. Acute and chronic prostate inflammation was coded as present or absent.[9,10] Chronic inflammation consisted mainly of lymphocytes and a variable number of plasma cells and macrophages. Acute inflammation consisted of neutrophilic infiltrate.

Patients were followed every 6 months at clinical visits, when peak urinary flow, PVR, I-PSS, CPSI and quality of life were determined. Medical and surgical history was also updated.

The protocol was approved by the institutional review board at each research site and all participants provided written informed consent. Of the 8,231 men enrolled in the study 4,126 (50.1%) were randomized to receive placebo and were included in study. We excluded 17 men (less than 1%) due to missing data on baseline acute and chronic inflammation, which resulted in a final study sample of 4,109.

Univariable comparisons of baseline characteristics between men with vs without baseline acute and chronic prostate inflammation were performed using the chi-square test for categorical data and the Student t-test for continuous variables. The association of acute and chronic baseline inflammation with CPSI scores at multiple time points were plotted and evaluated with the Student t-test. The association of acute and chronic inflammation in baseline prostate biopsies with time to