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QUERCETIN IN MEN WITH CATEGORY III CHRONIC PROSTATITIS: A PRELIMINARY PROSPECTIVE, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Objectives. The National Institutes of Health (NIH) category III chronic prostatitis syndromes (nonbacterial chronic prostatitis and prostatodynia) are common disorders with few effective therapies. Bioflavonoids have recently been shown in an open-label study to improve the symptoms of these disorders in a significant proportion of men. The aim of this study was to confirm these findings in a prospective randomized, double-blind, placebo-controlled trial.

Methods. Thirty men with category IIIa and IIIb chronic pelvic pain syndrome were randomized in a double-blind fashion to receive either placebo or the bioflavonoid quercetin 500 mg twice daily for 1 month. The NIH chronic prostatitis symptom score was used to grade symptoms and the quality-of-life impact at the start and conclusion of the study. In a follow-up unblind, open-label study, 17 additional men received 1 month of a supplement containing quercetin, as well as bromelain and papain (Prosta-Q), which enhance bioflavonoid absorption.

Results. Two patients in the placebo group refused to complete the study because of worsening symptoms, leaving 13 placebo and 15 bioflavonoid patients for evaluation in the blind study. Both the quercetin and placebo groups were similar in age, symptom duration, and initial symptom score. Patients taking placebo had a mean improvement in NIH symptom score from 20.2 to 18.8 (not significant), while those taking the bioflavonoid had a mean improvement from 21.0 to 13.1 ($P = 0.003$). Twenty percent of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement of symptoms of at least 25%. In the 17 patients who received Prosta-Q in the open-label study, 82% had at least a 25% improvement in symptom score.

Conclusions. Therapy with the bioflavonoid quercetin is well tolerated and provides significant symptomatic improvement in most men with chronic pelvic pain syndrome. UROLOGY **54:** 960–963, 1999. © 1999, Elsevier Science Inc.

The chronic prostatitis syndromes are a common problem in urologic practice, with much controversy concerning the pathophysiology and appropriate treatment.[1] Whether or not pathogens are cultured or white blood cells are found in the prostatic fluid, prolonged antibiotic therapy is common. When antimicrobial therapy is ineffective, many other forms of therapy, including alpha-blockers, anti-inflammatories, muscle relaxants, physiotherapy, and even surgery have been tried, with variable success. Both patient and urologist frustration with this disorder is very high.[2]

Quercetin is a naturally occurring bioflavonoid found in high concentrations in red wine, onions, and green tea. Documented properties include activity as an anti-oxidant, tyrosine kinase inhibitor, nitric oxide inhibitor, and anti-inflammatory through interference with NF-κB.[3] It has been reported that the use of oral bioflavonoids in men with chronic prostatitis resulted in a significant improvement in symptoms in 59% of the men.[4] In those patients in whom the prostate fluid cultures were negative, the improvement increased to 75% of the men. We wished to confirm these prelimi-

D. A. Shoskes and J. Rajfer own stock in companies that will benefit from sales of the supplements reported in this study.

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nary open-label findings in a prospective, randomized, placebo-controlled trial.

MATERIAL AND METHODS

Patients with chronic pelvic pain syndrome (CPPS) for at least 6 months were evaluated by history, physical examination, and examination and culture of expressed prostatic secretions, urethral swab, and first voided and midstream urine. The postmassage urine was omitted because prostatic fluid was obtained from all patients. Thirty patients without positive bacterial cultures localizing to the prostatic fluid were enrolled in the study after giving written informed consent. This study was approved by our institutional review board. Patients were randomized 1:1 in a double-blind fashion to receive either quercetin capsules 500 mg orally twice daily or placebo for 1 month. Patients who had previously used quercetin were excluded from the study. Both quercetin and placebo capsules were identical in appearance. The National Institutes of Health (NIH) chronic prostatitis symptom score[5] was administered at the start and conclusion of the study. This recently validated instrument for men with CPPS comprises nine questions covering pain, voiding dysfunction, and impact on quality of life.

After the randomized study was completed, an additional 17 patients were treated in an open-label fashion with a supplement (Prosta-Q, Farr Laboratories, Santa Clarita, Calif) containing quercetin, in addition to two other antioxidants, bromelain and papain; the latter two compounds are known to increase the absorption of bioflavonoids. In four of these Prosta-Q-treated patients, oxidant stress was assessed by measuring prostatic fluid levels of 8-iso-prostaglandin $F_{2\alpha}$ (Iso P) using an enzyme immunoassay kit (Caymen Chemicals). Results were expressed as picograms of Iso P per milliliter of prostatic fluid.

Statistical comparison between groups was performed with an unpaired *t* test and within groups over time with a paired *t* test. For category values, comparisons were performed with the chi-square test. Significance was set at $P < 0.05$.

RESULTS

All 15 patients randomized to quercetin completed the study; 2 of 15 patients randomized to placebo did not because of worsening symptoms. The final symptom scores of these 2 patients were not included in the analysis, but their lack of improvement was included. As seen in Table I, the groups did not differ significantly in age, symptom duration, initial number of white blood cells in the prostatic fluid, or NIH symptom score.

At the completion of the study, the mean symptom score improved from 21.0 to 13.1 in the quercetin group but from 20.2 to only 18.8 in the placebo group ($P = 0.003$) (Table I). This represented a mean improvement of 35% in the quercetin group versus 7.2% in the placebo group. The improvement in total score in men taking quercetin appeared to come from improvements in the pain score (10.3 to 6.2, $P = 0.005$) and quality-of-life score (8 to 4.9, $P = 0.004$) but not the urinary score (2.7 to 1.5, $P =$ not significant). It has been found that for our patients to consider their change in symptoms to be a meaningful improvement, the NIH symptom score must improve by at least 25%. Using this benchmark, 67% of quercetin patients had a significant improvement in symptoms versus 20% of the placebo patients ($P = 0.001$). Forty-seven percent of patients taking placebo had a worsening of the symptom score versus only 13% of the quercetin patients ($P = 0.05$). In the 17 patients with obtainable expressed prostatic secretions on both visits, the white blood cell count per high power field in the prostatic fluid decreased from a mean of 16.8 to 5.3 in the quercetin patients ($P = 0.01$) versus a decrease from 13.1 to 8.3 in the placebo patients (not significant) (Table I).

TABLE I. *Results for study and control patients*

	Placebo	Quercetin
Age (yr)	43.5 ± 3.7 (26–68)	46.2 ± 4.0 (26–72)
Symptom duration (yr)	11.5 ± 2.8 (2–35)	10.5 ± 2.8 (0.5–32)
Initial WBC/hpf	13.1 ± 4.4 (0–50)	16.9 ± 5.1 (0–50)
Final WBC/hpf	8.3 ± 4.6 (0–40) (n = 10)	2.9 ± 1.8 (0–10) (n = 7)
NIH score		
Pain		
Initial	9.4 ± 0.63 (6–12)	10.3 ± 0.86 (5–17)
Final	9.0 ± 0.88 (5–13)	6.2 ± 1.0 (0–13)
Urinary		
Initial	3.2 ± 0.76 (1–9)	2.7 ± 0.74 (0–11)
Final	3.0 ± 0.75 (1–9)	1.5 ± 0.5 (0–8)
Quality of life		
Initial	7.7 ± 0.74 (4–11)	8.0 ± 0.84 (3–12)
Final	6.8 ± 0.8 (4–11)	4.9 ± 0.69 (1–9)
Total score		
Initial	20.2 ± 1.1 (13–26)	21.0 ± 1.8 (12–39)
Final	18.8 ± 1.9 (12–33)	13.0 ± 1.7 (5–30)

KEY: WBC = white blood cells; hpf = high power field.
Data presented as mean ± standard error of the mean, with the range in parentheses.

In comparing the patients taking quercetin who significantly improved with therapy versus those who did not, no statistically significant difference between age (47 versus 46 years), starting NIH score (22.6 versus 17.8), or initial white blood cell count (16.6 vs 17.0) was found. The group that improved had a shorter mean duration of symptoms than the group that did not (6.5 versus 16.9 years), but there was a large overlap of ranges, with wide standard deviations in both groups, leading to a lack of statistical significance. The group that improved with quercetin included 1 man with a 20-year history of symptoms and 2 men with 10-year histories.

One patient taking placebo developed a rash that resolved when he stopped taking the capsules. One patient taking quercetin developed a headache after the first few doses, which resolved, and 1 pa-

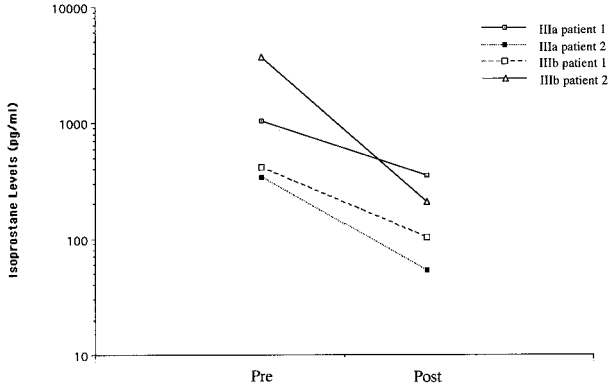

FIGURE 1. *Change in oxidative stress in prostatic fluid of men before (Pre) and after (Post) therapy with Prosta-Q for 1 month. Isoprostane results expressed as picograms per milliliter of fluid for 2 patients in NIH category IIIa and 2 patients in category IIIb.*

tient taking quercetin noted mild tingling of the extremities after each dose. All these side effects resolved after cessation of therapy.

Subsequently, 17 patients were treated in an open-label fashion with a combination supplement capsule that contained 500 mg quercetin, as well as bromelain and papain, at a dose of 1 tablet twice daily for 1 month. In these patients, the NIH symptom score improved from an average of 25.1 to 14.6, representing a mean improvement of 44%. In addition, 82% demonstrated at least a 25% improvement in symptom score. In 4 of these 17 patients, a sufficiently large sample of expressed prostatic fluid was available to assay for oxidant stress both before and after therapy by measuring levels of Iso P. As seen in Figure 1, all 4 patients demonstrated a large decrease in Iso P levels after treatment with the quercetin-based supplement (before 1365 ± 782 pg/mL versus after 179 ± 66.0 pg/mL, $P = 0.06$).

COMMENT

Patients with chronic prostatitis refractory to conventional therapies are a great challenge and frustration in urologic practice.[2] For those who do not respond to antibiotic therapy but have negative prostatic fluid cultures, the etiology is unclear. A proportion of these patients probably have true persistent bacterial infections; indeed, a significant proportion of men with culture-negative CPPS have positive bacterial signal in their prostatic fluid by 16S ribosomal RNA molecular techniques.[6] There is another subset of men with CPPS who have dysynergic voiding patterns seen on videourodynamic evaluation,[7] that may respond to biofeedback or therapy with alpha-blockers,[8] with or without antibiotic therapy.[9]

It has been theorized that CPPS may represent an inflammatory dysregulation of the injury response,[10] leading to persistent chemokine upregulation, immune cell infiltration, oxidant stress, and cellular injury. Therefore, if persistent infection is ruled out either by careful cultures or failure of appropriate antimicrobial therapy, therapy with agents that block chemokine production and oxidant stress may improve this condition.

Bioflavonoids are polyphenolic compounds found in plants, especially onions, spices, green tea, and red wine.[11] They have antioxidant properties, both as free radical scavengers[12] and as inhibitors of xanthine oxidase.[13] In addition, they have anti-inflammatory properties, blocking both chemokines and cytokines,[3,14,15] and they interfere with tyrosine kinase enzyme activation, inhibiting the division and growth of T cells[16] and prostate cancer cells.[17] Finally, they have antimicrobial[18] and antifungal properties,[19] which may have an impact on the CPPS patient population as well.

In an open-label, unblind study, it was reported that therapy with oral quercetin significantly reduced the symptoms of chronic prostatitis in 59% of patients.[4] When only patients whose prostatic fluid culture was completely sterile were analyzed, 75% derived improvement. We therefore chose to focus on this latter group of patients. In the current study, 67% of patients taking quercetin had a significant improvement in symptoms (at least 25%) versus 20% of the men taking placebo. All men with this degree of improvement elected to continue taking quercetin. Unfortunately, we were unable to complete a true crossover design, as only 4 placebo patients elected to take a further month of capsules known to have quercetin. Although 3 of these 4 did have significant improvement in symptoms, no statistical conclusions can be drawn with these modest numbers.

Although the symptomatic response of patients taking quercetin is significant, few patients became completely asymptomatic. Severe urinary symptoms in particular were least likely to improve with quercetin alone; however, once pain was controlled, urinary symptoms were often responsive to alpha-blockers or anticholinergics. Variable absorption may be another issue in patients with a partial response to quercetin. Dietary quercetin has variable absorption depending on the source and degree of glycosylation.[20] Cellular bioavailability may be further compromised by tight binding to plasma proteins, especially albumin.[21] It was for this reason that we empirically examined the effects of a combination of quercetin, papain, and bromelain in an attempt to enhance transport of the bioflavonoid across the intestinal membrane.[22] In this unblind, open-label study, there was a superior impact on symptom score, percentage of improvement, and percentage of patients with at least

a 25% improvement compared with the pure quercetin capsules alone.

Although the exact mechanism of action of quercetin in improving the symptoms of men with chronic prostatitis is not known, in all 4 patients taking the quercetin-papain-bromelain combination who were so tested, large decreases in prostatic fluid isoprostane levels, a presumed marker of oxidative stress in the prostate, were found. Treatment with quercetin may therefore prevent oxidative-mediated cellular injury, whether instigated by an infective, inflammatory, or auto-immune mechanism.

Few therapies have shown durable efficacy in men with CPPS. In men with negative cultures in whom antibiotic therapy has failed, varying degrees of success have been reported with nonsteroidal anti-inflammatories,[23] physiotherapy with biofeedback,[24] thermotherapy,[25] alpha-blockers,[9] and prostatic massage.[26] By comparison, our study suggests that therapy with a supplement containing quercetin is efficacious, inexpensive, well tolerated, and safe. The only theoretical drug interaction is with quinolone antibiotics. Since quercetin binds in vitro to the DNA gyrase site on bacteria,[18] it may serve as a competitive inhibitor to quinolones, which also bind to this site.

In conclusion, therapy with quercetin gave significant symptomatic relief with minimal side effects compared with placebo in men with nonbacterial CPPS. The ideal formulation, dosage regimen, and long-term durability of the response is yet to be determined.

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