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Original Contribution

Associations Between C-Reactive Protein and Benign Prostatic Hyperplasia/ Lower Urinary Tract Symptom Outcomes in a Population-based Cohort

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Inflammation may play a role in the development of benign prostatic hyperplasia and/or lower urinary tract symptoms (LUTS). Higher levels of C-reactive protein (CRP) may therefore be associated with the development of these outcomes. The authors examined the association of CRP levels measured in 1996 with rapid increases in prostate volume, prostate-specific antigen levels, and LUTS as well as rapid decreases in peak flow rates (through 2005) in a population-based cohort of men residing in Olmsted County, Minnesota. Men with CRP levels of $\geq$3.0 mg/L were more likely to have rapid increases in irritative LUTS (odds ratio (OR) = 2.14, 95% confidence interval (CI): 1.18, 3.85) and rapid decreases in peak flow rates (OR = 2.54, 95% CI: 1.09, 5.92) compared with men with CRP levels of $<$3.0 mg/L. CRP levels were not significantly associated with rapid increases in prostate volume, obstructive LUTS, or prostate-specific antigen levels. Associations were attenuated after adjusting for age, body mass index, hypertension, and smoking history (irritative LUTS: OR = 2.00, 95% CI: 1.04, 3.82; peak flow rate: OR = 2.45, 95% CI: 0.73, 8.25). These results suggest that rapid increases in irritative LUTS and rapid decreases in peak flow rates may be due to inflammatory processes.

C-reactive protein; inflammation; prostatic hyperplasia; signs and symptoms; urinary tract

Abbreviations: BPH, benign prostatic hyperplasia; CRP, C-reactive protein; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen.

Editor's note: *An invited commentary on this article appears on page 1291, and the authors' response is published on page 1294.*

Inflammatory processes may play a role in the development of histologic benign prostatic hyperplasia (BPH) among aging men (1). Acute and chronic inflammatory infiltrates have been routinely found in prostate tissue specimens obtained from men with BPH (2–4), and greater levels of inflammation have been observed in larger prostates (3, 5). Additionally, an increased risk of acute urinary retention has been found for men with evidence of prostatic inflammation (5–8). Together, these studies suggest that prostatic inflammation may play an important role in prostatic growth and eventual development of acute urinary retention.

The role of inflammation in the development of lower urinary tract symptoms (LUTS) has been less well studied. Minor associations between prostatic inflammation and LUTS have been observed (5, 9), but it has been noted that the correlations may not be clinically significant. Because correlations between BPH and LUTS are modest (10–14), and because LUTS may develop in the absence of histologic BPH, in such cases, prostatic inflammation may not directly influence the development of LUTS. However, it is also possible that inflammation in other components of the urogenital system (such as the urethra or the bladder) may play a role in the development of LUTS even in the absence of prostatic hyperplasia.

C-reactive protein (CRP) is a nonspecific marker of systemic inflammation, and it may reflect the presence of inflammation in urologic pathways that could lead to the

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development of BPH and/or LUTS. In support of this hypothesis, Rohrmann et al. (15) conducted a cross-sectional study examining the association between CRP levels and the presence of LUTS among men participating in the Third National Health and Nutrition Examination Survey (NHANES III). These investigators found a modest association between CRP level and LUTS, but it was not possible to assess the association between CRP and prostate volume. Additionally, because these data were cross-sectional, they were unable to determine whether elevated CRP levels preceded the development of LUTS. To build on this previous work, we took advantage of longitudinal data available through the Olmsted County Study of Urinary Symptoms and Health Status among Men to determine whether men with elevated CRP levels were more likely to experience rapid increases in prostate volume, prostate-specific antigen (PSA) levels, and LUTS and rapid decreases in peak urinary flow rates compared with men with lower levels of CRP.

MATERIALS AND METHODS

Study population

Details related to the study population have been previously published (16, 17). Briefly, a cohort of Caucasian men aged 40–79 years was randomly selected from an enumeration of the 1990 Olmsted County, Minnesota, population. Men who had a history of prostate or bladder surgery, urethral surgery or stricture, or medical or other neurologic conditions that could affect normal urinary function were excluded. After we excluded men with these preexisting conditions, 3,874 men were asked to join the study, and 2,115 (55%) agreed to participate.

Participants completed a previously validated baseline questionnaire that assessed LUTS severity from questions similar to those in the American Urological Association symptom index (18), and a composite symptom index score was estimated (16). Participants also voided into a portable urometer to measure peak urinary flow rate. A 25% random subsample of men was invited to participate in a detailed in-clinic urologic examination including transrectal sonographic imaging to determine prostate volume and serum PSA measurement.

The cohort was followed biennially for 16 years by using a protocol similar to the initial examination. During the second and third round of visits (1992 and 1994, respectively), men who did not participate in the follow-up were replaced by men randomly selected from the community ($n = 229$ and $n = 103$, respectively). Of the replacement men, 100 and 58 were added to the in-clinic subset in the second and third rounds, respectively. Since that time, the study has been maintained as a closed cohort. The present study focuses on the men who participated in the in-clinic portion of the study.

Assessment of CRP

Frozen serum samples from men who participated in the in-clinic portion of the study during the sixth year of follow-up (1996) were used to measure CRP levels ($n = 442$). Four rounds of follow-up were completed after 1996. CRP levels were assessed by using a high-sensitivity, latex particle enhanced immunoturbidimetric assay (Diasorin Inc., Stillwater, Minnesota) at the Mayo Clinic Immunochemical Core Laboratory. The lower limit of detection was 0.10 mg/L. Within-run and between-run coefficients of variation ranged from 0.7% to 3.6%. CRP cutpoints at the <25th, 25th–<50th, 50th–<75th, and ≥75th percentiles were examined. A cutpoint of ≥3.0 mg/L was then used for the remaining analyses because CRP levels in this range have been shown to be strongly associated with the development of coronary heart disease (19), this cutpoint has been used in examining associations between CRP and LUTS (15), and it was very similar to the upper 75th percentile of the CRP distribution in our study population (upper 75th percentile, ≥2.9 mg/L).

Outcome measurements

LUTS were measured by a previously validated questionnaire analogous to the American Urological Association symptom index (18, 20, 21). Peak urinary flow rates were measured electronically by using a Dantec 1000 urometer (Dantec Medical, Santa Clara, California). A minimum voided volume of 150 mL was necessary for obtaining a valid peak flow rate (22, 23).

Serum PSA levels were determined with the Tandem-R PSA assay (Hybritech Inc., San Diego, California). The serum samples were obtained prior to any prostatic manipulations, including digital rectal examination and transrectal ultrasound (24).

Total prostate volume was measured via transrectal ultrasound by using a 7.5-MHz biplanar endorectal transducer. In addition to assessment of the echogenic pattern of the prostate gland, 3 measurements were made to calculate total prostatic volume. Anterior-posterior and transverse diameters were measured at the maximal dimensions, and the superior-inferior diameter was measured at the maximal length from the base to the apex of the midline sagittal plane (25, 26).

Linear mixed-effects regression models were used to estimate annual longitudinal changes in LUTS, peak urinary flow rate, PSA level, and total prostate volume by regressing each measure on time from initial visit and 10-year age groups (11, 23, 25, 27, 28). An interaction term was included to allow for different slopes across age groups. An overall annual rate of change (slope) for each man was determined by combining the average longitudinal changes (fixed effects) with the individual changes (random effects) (29, 30). Similarly, both fixed and random effects allowed determination of an overall baseline intercept for each decade of age and allowed for offsets for each man. Observations after treatments for BPH/LUTS (surgical, medical, or use of herbal medications) or diagnosis of prostate cancer were censored. Because of skewed distributions, a log transformation was applied to peak flow rate, PSA, and total prostate volume measurements before slope determination; therefore, the slopes represent the percentage change per year assuming an exponential growth curve. Symptom score slopes represent the absolute change per year in score. Rapid increases were defined as the upper 10th percentile of the LUTS, PSA level, and total prostate volume slope distributions, while rapid decreases in peak

Table 1. Characteristics of the Population of Men Studied Regarding Associations Between CRP Levels and BPH/LUTS, Minnesota, 1996

Participant Characteristic	No.	%
Age, years		
40–49	112	25.34
50–59	148	33.48
60–69	105	23.76
≥70	77	17.42
CRP level, mg/L		
<3.0	341	77.15
≥3.0–<5.5	55	12.44
≥5.5–<8.0	23	5.20
≥8.0	23	5.20
LUTS symptom index score		
<7	219	49.55
7–19	202	45.70
≥20	21	4.75
Irritative LUTS symptom index score		
≤3	223	50.45
>3	219	49.55
Obstructive LUTS symptom index score		
≤4	270	61.09
>4	171	38.69
Peak urinary flow rate, mL/second		
≥12	317	71.72
<12	108	24.43
Prostate volume, mL		
≤30	232	52.49
>30	161	36.43
PSA level, ng/mL		
≤1.4	288	65.16
>1.4	154	34.84
Body mass index, kg/m^2		
<25	74	16.74
25–29	191	43.21
≥30	150	33.94
Diabetes (baseline)		
No	426	96.38
Yes	16	3.62
Hypertension (baseline)		
No	349	78.96
Yes	92	20.81
Smoking history (prior to 1996)		
No	168	38.01
Yes	274	61.99
Alcohol consumption (baseline)		
<Once/week	195	44.12
≥Once/week	203	45.93
NSAID use (prior to 1996)		
No	272	61.54
Yes	170	38.46

Abbreviations: BPH, benign prostatic hyperplasia; CRP, C-reactive protein; LUTS, lower urinary tract symptoms; NSAID, nonsteroidal antiinflammatory drug; PSA, prostate-specific antigen.

urinary flow rate were defined as the lower 10th percentile of the slope distribution.

Assessment of other patient characteristics

Self-report of diabetes, hypertension, and alcohol consumption (<once/week vs. ≥once/week) was obtained from baseline questionnaires. Body mass index (measured in 1996) was categorized as <25 kg/m^2 (normal), 25–29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese). Men who reported smoking or daily use of nonsteroidal antiinflammatory drugs at any time prior to 1996 were classified as ever smokers or ever users of these drugs, respectively.

Statistical analyses

Median CRP levels were compared across participant characteristic categories by using the Kruskal-Wallis test. Bivariate and multivariable logistic regression analyses were used to assess the association of elevated CRP level with rapid increases in LUTS, prostate volume, and PSA and rapid decreases in peak urinary flow rate. Logistic regression models examining the associations between CRP levels and rapid changes in BPH/LUTS outcomes were adjusted for age and other potential confounders including body mass index, hypertension, and smoking history. Interaction terms were created and were included in the logistic models to examine potential effect modification by third variables.

Cox proportional hazards models were used to determine whether CRP level in 1996 was associated with risk of a high absolute change in each BPH/LUTS outcome. Absolute changes were calculated from 1996 to each follow-up round. High absolute change in each of the outcomes was defined as follows: the upper 25th percentile of change for LUTS (increase of >7 points), irritative LUTS (increase of >3 points), obstructive LUTS (increase of >4 points), prostate volume (increase of >14.77 mL), and PSA level (increase of >1.24 ng/mL); and the lower 25th percentile of change in peak flow rates (decrease of >10.50 mL/second). Models were adjusted for age and other potential confounders.

RESULTS

Characteristics of the study population in 1996 are shown in Table 1. CRP levels were available for 442 (95%) of the men participating in the in-clinic cohort in 1996 (mean age,

Table 2. Spearman Correlations Between CRP Level in 1996 and Overall Changes in BPH/LUTS Outcomes (Slopes) for Men in Minnesota

BPH/LUTS Outcome Slope	Unadjusted (*R*, *p*)[a]	Age Adjusted (*R*, *p*)
LUTS	0.04, 0.42	−0.01, 0.87
Irritative LUTS	0.06, 0.25	0.01, 0.87
Obstructive LUTS	0.03, 0.57	−0.01, 0.79
Peak urinary flow rate	−0.03, 0.54	0.07, 0.12
Prostate volume	0.01, 0.79	0.01, 0.85
PSA	0.07, 0.16	0.02, 0.63

Abbreviations: BPH, benign prostatic hyperplasia; CRP, C-reactive protein; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen.

[a] *R*, Spearmen correlation coefficient; *p*, significance level.

59.0 years; standard deviation, 10.3). The median CRP level was 1.4 mg/L (interquartile range, 0.7–2.9). Overall correlations between CRP levels and BPH/LUTS outcome slopes were not statistically significant (Table 2). It is possible, however, that elevated CRP levels are associated with only rapid changes in the BPH/LUTS outcomes. Therefore, we examined the associations between CRP and various slope cutpoints, and we present in this paper the data for the associations between CRP levels and the 10th percentile cutpoints for each of the outcomes of interest. The changes represented by the 10th percentile cutpoints are shown in Table 3. For example, rapidly changing LUTS scores (the upper 10th percentile of the distribution in LUTS slopes) increased by 0.57 points per year.

CRP levels were higher in older men, men with rapid increases in irritative LUTS, and men with rapid decreases in peak urinary flow rates (Table 4). Additionally, CRP levels were significantly greater among those with higher body mass indexes, those who had ever smoked, and those with hypertension (Table 4).

Men with CRP levels of $\geq$2.9 mg/L were more likely to have rapid increases in irritative LUTS and more rapid decreases in peak urinary flow rates compared with men with lower CRP levels. The associations between CRP level and rapid changes in irritative LUTS and peak urinary flow rates strengthened as CRP levels increased (*P* test for trend = 0.01; Table 5).

Table 3. Upper 10th Percentile Cutpoint Used to Assess Rapid[a] Changes in BPH/LUTS Outcomes Over Time for Men in Minnesota

Rapid Changes in Outcomes	Change
LUTS, score/year	0.57
Irritative LUTS, score/year	0.22
Obstructive LUTS, score/year	0.35
Peak urinary flow rate, %/year[b]	−5.8
Prostate volume, %/year	3.5
PSA, %/year	6.6

Abbreviations: BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen.

[a] The LUTS measures are the raw changes in symptom score per year; peak urinary flow rate, prostate volume, and PSA are all percentage changes per year.

[b] The lower (vs. upper) 10th percentile cutpoint was used.

The effects of age, body mass index, hypertension, and smoking history on the associations between elevated CRP and changes in BPH/LUTS outcomes were also examined. Associations between higher CRP levels and more rapid changes in irritative LUTS and peak urinary flow rates decreased slightly after adjusting for age, but they strengthened slightly after adjusting for body mass index, hypertension, and smoking history (Table 6). Stratified analyses were conducted to determine whether these variables might modify the association between CRP and rapid changes in the outcomes. Interaction terms were not statistically significant, but associations between elevated CRP and rapid changes in irritative LUTS were stronger among older men and men with higher body mass indexes (Table 7). Associations between elevated CRP and rapid decreases in peak flow rates were also stronger among men with higher body mass indexes and among men with hypertension, but interactions were again not statistically significant (Table 7).

Finally, the risks of developing high absolute changes in the BPH/LUTS outcomes among men who had higher CRP levels in 1996 were examined. Median follow-up ranged from 9.67 to 9.84 years, depending on the outcome examined. CRP levels were not significantly associated with risk of developing high absolute changes in the BPH/LUTS outcomes during subsequent rounds of follow-up (Table 8).

DISCUSSION

Our data indicate that men with higher levels of the nonspecific inflammatory marker CRP were approximately 2 times more likely to have rapid worsening of irritative urinary LUTS and almost 2.5 times more likely to have rapidly decreasing urinary flow rates. However, men with elevated CRP levels were not more likely to experience rapid increases in prostate volume, obstructive LUTS, or PSA level.

CRP levels rise rapidly during acute inflammation, and elevated levels are also a marker for chronic inflammation (31). As such, CRP levels might represent a marker for prostatic inflammation. If inflammation in the prostate leads to prostatic growth, and if systemic CRP levels reflect prostatic inflammation, correlations between CRP levels and rapid changes in prostatic growth might be observed. However, in this population, we did not observe associations between higher CRP levels and rapid increases in prostate volume. Additionally, we did not observe a significant association between CRP level and rapid increases in obstructive LUTS. These results do not discount the possibility that inflammatory processes in the prostate are associated with prostatic growth; however, they do suggest that rapid growth in the prostate is not necessarily reflected in systemic levels of CRP.

We did observe associations between CRP levels and rapid changes in irritative LUTS and urinary flow rates. These results are similar to those obtained in the cross-sectional study by Rohrmann et al. (15), who observed a nonsignificant association between higher CRP levels and presence of

Table 4. Median CRP Levels in 1996 Among Study Participants With Specific Characteristics, Minnesota

Participant Characteristic	No.	CRP Level, Median (IQR), mg/L	Kruskal-Wallis *P* Value
Age, years			0.04
40–49	112	1.3 (0.5–2.7)	
50–59	148	1.4 (0.7–2.6)	
60–69	105	1.5 (0.8–3.2)	
≥70	77	1.8 (0.8–4.2)	
LUTS slope			0.31
Lower 90th percentile	380	1.3 (0.7–2.7)	
Upper 10th percentile (rapid change)	59	2.1 (0.7–3.7)	
Irritative LUTS slope			0.01
Lower 90th percentile	381	1.3 (0.7–2.6)	
Upper 10th percentile (rapid change)	58	2.3 (0.9–4.5)	
Obstructive LUTS slope			0.77
Lower 90th percentile	380	1.4 (0.7–2.7)	
Lower 10th percentile (rapid change)	59	2.0 (0.5–3.4)	
Peak urinary flow rate slope			0.01
Upper 90th percentile	415	1.4 (0.7–2.8)	
Upper 10th percentile (rapid change)	24	2.5 (0.9–6.8)	
Prostate volume slope			0.52
Lower 90th percentile	382	1.4 (0.7–2.8)	
Upper 10th percentile (rapid change)	56	1.4 (0.7–3.2)	
PSA slope			0.56
Lower 90th percentile	388	1.3 (0.7–2.8)	
Upper 10th percentile (rapid change)	51	1.7 (0.7–3.2)	
Body mass index, kg/m^2			<0.0001
<25	74	0.8 (0.4–1.9)	
25–29	191	1.2 (0.7–2.7)	
≥30	150	2.1 (1.1–3.3)	
Diabetes (baseline)			0.82
No	426	1.4 (0.7–2.9)	
Yes	16	1.4 (0.6–3.1)	
Hypertension (baseline)			<0.0001
No	349	1.3 (0.6–2.7)	
Yes	92	2.1 (1.2–3.7)	
Smoking history (prior to 1996)			0.03
No	168	1.2 (0.6–2.6)	
Yes	274	1.6 (0.7–3.2)	
Alcohol consumption (baseline)			0.80
<Once/week	195	1.6 (0.7–3.0)	
≥Once/week	203	1.4 (0.8–2.9)	
NSAID use (prior to 1996)			0.93
No	272	1.5 (0.7–2.8)	
Yes	170	1.3 (0.7–2.9)	

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; LUTS, lower urinary tract symptoms; NSAID, nonsteroidal antiinflammatory drug; PSA, prostate-specific antigen.

Table 5. Results of Logistic Regression Using CRP Level in 1996 to Predict the Odds of Rapid Changes[a] in BPH/LUTS Outcomes Among Men in Minnesota

Rapid Changes in Outcomes	CRP <0.68 mg/L (<25th Percentile)	CRP ≥0.68–<1.38 mg/L (≥25th–<50th Percentile)		CRP ≥1.38–<2.85 mg/L (≥50th–<75th Percentile)		CRP ≥2.85 mg/L (≥75th Percentile)		*P* Test for Trend
		OR	95% CI	OR	95% CI	OR	95% CI	
LUTS	Reference	0.52	0.22, 1.24	0.67	0.29, 1.51	1.54	0.76, 3.10	0.16
Irritative LUTS	Reference	1.00	0.41, 2.41	1.02	0.42, 2.46	2.62	1.22, 5.63	0.01
Obstructive LUTS	Reference	0.79	0.36, 1.73	0.53	0.23, 1.27	1.37	0.67, 2.79	0.50
Peak urinary flow rate	Reference	7.41	0.90, 61.26	4.19	0.46, 38.13	13.21	1.69, 103.46	0.01
Prostate volume	Reference	1.18	0.53, 2.61	0.85	0.36, 1.98	1.36	0.63, 2.96	0.60
PSA	Reference	0.73	0.29, 1.80	1.32	0.59, 2.96	1.28	0.57, 2.87	0.32

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; CRP, C-reactive protein; LUTS, lower urinary tract symptoms; OR, odds ratio; PSA, prostate-specific antigen.

[a] Rapid change is defined as being in the upper 10th percentile (or lower 10th percentile for peak urinary flow rate) of the slope distributions.

LUTS. These investigators suggested that elevated CRP levels could reflect development of BPH and subsequent development of LUTS. However, they were not able to determine whether elevated CRP levels in their population were associated with increased prostate volume. In our study, we found no associations between CRP level and increases in prostate volume. However, LUTS can develop even in the absence of prostatic enlargement, and our data suggest inflammatory processes may play a role in the development of irritative LUTS and decreased urinary flow rates. Further studies examining inflammation in other components of the urogenital system (such as the bladder) may contribute to understanding how a systemic marker for inflammation might be associated with development of LUTS and decreased urinary flow rate.

A number of characteristics have been found to be associated with elevated CRP levels, and, because some are also associated with BPH and/or LUTS, such characteristics may have explained the associations we observed between CRP levels and BPH/LUTS outcomes. In particular, body mass index has been strongly associated with elevated CRP levels (32, 33), whereas weight loss has been associated with a decline in CRP (34). Elevated levels have also been associated with smoking (35, 36), metabolic syndrome (37–40), and hypertension (41). Although the data are conflicting, presence of diabetes and components of the metabolic syndrome have also sometimes been associated with BPH and/or LUTS (42–45). In our study, older age, elevated body mass index, and self-reported smoking and hypertension were associated with higher CRP levels and could have represented potential confounders of the associations between CRP level and rapid changes in BPH/LUTS outcomes. However, after adjusting for these variables, our results were only slightly attenuated, suggesting that these variables do not explain the observed associations.

Rohrmann et al. (15) also found that the association between CRP and LUTS was attenuated among men without metabolic syndrome, and they suggested that metabolic syndrome may mediate inflammation leading to the development of LUTS (15). To address this possibility in our population, we performed stratified analyses to examine potential interactions between elevated CRP and age, body mass index, diabetes, hypertension, smoking history, alcohol consumption, and nonsteroidal antiinflammatory drug use. Interaction terms were not statistically significant. We lacked data on blood pressure measurements and on fasting glucose, cholesterol, and lipid levels, so we were not able to rigorously

Table 6. Results of Logistic Regression Using CRP Level in 1996 to Predict the Odds of Being in the Upper 10th Percentile of the Slope Distributions of BPH/LUTS Outcomes, With a CRP Level of ≥3.0 mg/L, for Men in Minnesota

Rapid Changes in Outcomes	Unadjusted		Age Adjusted		Multivariable Adjusted[a]	
	OR	95% CI	OR	95% CI	OR	95% CI
LUTS	1.57	0.86, 2.88	1.35	0.73, 2.52	1.49	0.77, 2.87
Irritative LUTS	2.14	1.18, 3.85	1.85	1.01, 3.39	2.00	1.04, 3.82
Obstructive LUTS	1.43	0.77, 2.63	1.23	0.66, 2.30	1.25	0.64, 2.41
Peak urinary flow rate[b]	2.54	1.09, 5.92	1.89	0.68, 5.23	2.45	0.73, 8.25
Prostate volume	1.15	0.60, 2.20	1.04	0.53, 2.01	0.81	0.40, 1.66
PSA	1.17	0.59, 2.29	1.05	0.53, 2.09	1.06	0.51, 2.20

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; CRP, C-reactive protein; LUTS, lower urinary tract symptoms; OR, odds ratio; PSA, prostate-specific antigen.

[a] Adjusted for age, body mass index, hypertension, and smoking history.

[b] The lower (vs. upper) 10th percentile cutpoint was used.

Table 7. Potential Modifiers of the Association Between Elevated CRP Level (≥3.0 mg/L in 1996) and Rapid Increases in Irritative LUTS and Decreases in Peak Flow Rate Using Logistic Regression to Predict the Odds of Being in the Upper 10th Percentile of the Irritative LUTS Slope Distribution (the Lower 10th Percentile of the Peak Urinary Flow Rate Slope Distribution), Stratified by Various Third Variables, for Men in Minnesota

Variable	Rapid Changes in Irritative LUTS		Interaction-term *P* Value	Rapid Changes in Peak Urinary Flow Rate		Interaction-term *P* Value
	OR	95% CI		OR	95% CI	
Age, years						
<70	1.54	0.73, 3.26	0.25			
≥70	3.33	1.13, 9.86		1.89	0.68, 5.23	
Body mass index, kg/m^2						
<25	0.94	0.18, 4.95	0.42	1.16	0.12, 11.00	0.69
25–29	2.59	1.04, 6.47		2.65	0.71, 9.88	
≥30	3.38	1.20, 9.46		4.04	0.65, 25.09	
Diabetes						
No	2.54	1.39, 4.65		2.46	1.02, 5.95	0.81
Yes				3.67	0.17, 77.55	
Hypertension						
No	2.27	1.14, 4.53	0.78	1.76	0.59, 5.23	0.34
Yes	1.88	0.58, 6.03		4.35	0.96, 19.68	
Smoking history						
No	3.74	1.21, 11.51	0.21	1.97	0.36, 10.69	0.77
Yes	1.62	0.81, 3.24		2.65	0.98, 7.16	
Alcohol consumption						
<Once/week	2.80	1.17, 6.69	0.50	2.84	0.90, 8.90	0.79
≥Once/week	1.86	0.80, 4.33		2.23	0.60, 8.25	
NSAID use						
No	1.82	0.83, 4.01	0.54	3.56	1.00, 12.73	0.50
Yes	2.64	1.08, 6.49		1.98	0.62, 6.29	

Abbreviations: CI, confidence interval; CRP, C-reactive protein; LUTS, lower urinary tract symptoms; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio.

determine whether associations between CRP levels and our outcomes were strongest among men with metabolic syndrome. However, point estimates of the associations of elevated CRP with rapid changes in irritative LUTS and peak flow rates were higher among men with higher body mass indexes. Additionally, the association between elevated CRP and rapid decrease in peak flow rate was also stronger among men with self-reported hypertension. Our data therefore lend some support to the hypothesis that metabolic syndrome may mediate inflammatory processes associated with some adverse urologic events. However, our data were underpowered to examine interactions, and observed associations were not completely consistent. For example, the association between elevated CRP and rapid changes in irritative LUTS was stronger among men without hypertension.

We did not find associations between CRP and overall changes in each of the outcomes examined. Additionally, we found no associations between CRP levels and high absolute changes in the BPH/LUTS outcomes, regardless of the CRP cutpoints examined. Our definition of ''high absolute change'' was less extreme than our definition of the upper (or lower) 10th percentile of rapid changes over time, and it is possible that higher levels of inflammation are associated with only more extreme changes in BPH/LUTS outcomes. Our associations were attenuated when we examined those between CRP levels and the upper 20th percentile of the outcome slopes rather than the upper 10th percentile of the outcome slopes. For example, we found that the association between having a CRP level of ≥3.0 mg/L and the odds of being in the upper 20th percentile of the slope distribution for irritative LUTS and the lower 20th percentile of the slope distribution for peak flow rate were 1.43 (95% confidence interval: 0.87, 2.34) and 2.01 (95% confidence interval: 1.18, 3.41), respectively.

Alternatively, the lack of concordance between the results from the Cox and logistic models may be due to the different outcomes we examined. Logistic regression models assess the association between CRP levels and extremes of the overall rate of progression (worsening) of the LUTS/BPH measures. By contrast, the proportional hazards models

Table 8. Hazard Ratios and 95% Confidence Intervals Predicting High Absolute Change in BPH/LUTS Outcomes Among Men With CRP Levels of ≥3.0 mg/L in 1996, Minnesota[a]

BPH/LUTS Outcome	Median Follow-up, Years	Unadjusted		Multivariable Adjusted[b]	
		HR	95% CI	HR	95% CI
LUTS increase of >7 points	9.84	1.05	0.61, 1.81	0.94	0.52, 1.69
Irritative LUTS increase of >3 points	9.84	1.21	0.73, 1.99	1.12	0.66, 1.90
Obstructive LUTS increase of >4 points	9.84	0.93	0.57, 1.51	0.86	0.52, 1.44
Peak flow rate decrease of >10.50 mL/second	9.71	1.02	0.63, 1.67	0.91	0.56, 1.50
Prostate volume increase of >14.77 mL	9.74	1.09	0.67, 1.76	0.79	0.47, 1.33
PSA increase of >1.24 ng/mL	9.67	1.21	0.76, 1.92	1.21	0.75, 1.95

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen.

[a] High absolute change cutpoints were determined as being in the upper 25th percentile (lower 25th percentile for peak urinary flow rate) of the maximum change distribution for each variable.

[b] Adjusted for age, body mass index, hypertension, and smoking history.

assess associations between CRP levels and time to occurrence of an extreme measure of LUTS/BPH. It is possible that outcomes in the logistic regression models include some men who started with low symptoms, high flow rate, or small prostates and have been progressing rapidly but have not reached the absolute cutpoints. Similarly, the proportional hazards models would include very short times to progression to the severe cutpoint for men who started near the cutpoint. In addition, the logistic regression models may include some "regression to the mean," and it could be that CRP may have value as an early indicator of men who are going to have problems (before they get to the absolute cutpoints).

Strengths of our study include the availability of longitudinal data, which allowed us to determine whether CRP levels at a specific time point were associated with changes in urologic measures over time. Additionally, data were available on a number of different urologic outcomes, including prostate volume, LUTS, and peak urinary flow rate, which enabled us to determine that CRP levels were associated with some of these outcomes but not others. Finally, we had extensive data on participant characteristics, which we were able to examine for potential confounding effects.

Potential limitations of our study include the availability of CRP levels at only one point in time. Ideally, we would have liked to obtain levels at baseline for each man, and longitudinally at each follow-up point, to assess whether baseline levels, or changes in CRP levels, preceded development of the BPH/LUTS outcomes of interest. Additionally, CRP is a nonspecific marker of inflammation and is routinely transiently elevated in those with acute illnesses and injuries (46). We were not able to determine whether the men in our study had acute conditions at the time the serum samples were obtained, which likely resulted in misclassification of CRP exposure. However, misclassification of this exposure would likely have biased our associations toward the null; therefore, the estimates of association in this paper may be conservative. Information on diabetes or hypertension was not available for our study population in 1996, and more men likely developed these conditions after initial study enrollment, resulting in potential misclassification. However, adjustment for baseline hypertension and body mass index actually strengthened associations between CRP and the LUTS/BPH outcomes (Table 6), suggesting that our reported associations may be underestimations of the true associations. Our study population was limited to Caucasian men, and our results may not be generalizable to other populations.

Because we examined multiple endpoints in this study, there is a possibility that our results are due only to type 1 error. However, our a priori hypotheses were that CRP levels may have been associated with changes in each of the outcomes that we examined. Because all of the outcomes reflect different aspects of the condition currently labeled BPH/LUTS, which likely has multiple etiologic components, we specifically analyzed these outcomes to determine whether CRP levels were associated with some outcomes and not others. Our results therefore suggest that inflammatory processes reflected by serum CRP levels are more associated with irritative symptoms and decreased urinary flow rate but not increases in prostatic volume.

Our data indicate that a nonspecific marker of systemic inflammation, CRP, was not associated with change in prostate volume but was associated with rapid increases in irritative LUTS and rapid decreases in urinary flow rate, suggesting that inflammatory processes may play a role in the development of these outcomes. While elevated CRP levels are currently used primarily as a marker for risk of heart disease, our data suggest that elevated levels may also indicate when a man is at increased risk of rapidly worsening urinary symptoms.

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