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Research Article

Musculoskeletal Pain, a Possible Indicator of Central Sensitization, Is Positively Associated With Lower Urinary Tract Symptom Progression in Community-Dwelling Older Men

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Abstract

Background: Musculoskeletal pain, a possible marker of central sensitization, is associated with higher prevalence of lower urinary tract symptoms (LUTS) among older men. We investigated whether musculoskeletal pain is associated with LUTS progression.

Methods: Participants were 5 569 men age ≥65 years enrolled in the prospective, multicenter Osteoporotic Fractures in Men (MrOS) Study. Self-reported musculoskeletal pain within 12 months before baseline was categorized as any pain and multilocation pain. Pain interference within 4 weeks of baseline was assessed with the SF-12 questionnaire. LUTS were assessed repeatedly with the American Urological Association Symptom Index (AUA-SI). Men with severe LUTS at baseline were excluded. LUTS progression was defined as the first occurrence of a ≥4-point AUA-SI increase during a 2-year follow-up interval. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were estimated using multivariable pooled logistic regression.

Results: LUTS progression was 37% higher among men with any musculoskeletal pain compared with men without pain (IRR 1.37, 95% CI: 1.21, 1.54). Positive associations were also observed between LUTS progression and pain at 1 (IRR 1.31, 95% CI: 1.13, 1.48) and ≥2 locations (IRR 1.42, 95% CI: 1.24, 1.60). Compared with men without pain interference, men with quite a bit/extreme pain interference were most likely to experience LUTS progression (minimal interference IRR 1.15, 95% CI: 1.03, 1.26; moderate interference IRR 1.28, 95% CI: 1.11, 1.45; quite a bit/extreme interference IRR 1.47, 95% CI: 1.22, 1.71).

Conclusions: Among men initially without severe LUTS, musculoskeletal pain is associated with an increased risk of LUTS progression. Studies using validated measures of central sensitization and LUTS progression among men are warranted.

Keywords: Aging, Central Nervous System Sensitization, Epidemiology

Approximately 25% of U.S. adults older than 50 years experience lower urinary tract symptoms (LUTS) (1). LUTS are a constellation of symptoms experienced during storage or voiding of urine. Not only are LUTS associated with psychological distress and decreased quality of life (2), they are associated with greater risk of falls among older men (3). Symptoms often worsen over time (4) and, in a substantial proportion of people, LUTS do not respond to pharmacologic treatment (5,6). The variable response to pharmacologic interventions that target the lower urinary tract suggests that, for some individuals, LUTS may be a manifestation of non-LUT causes that require a different approach to care (7). Despite their high prevalence and health impact among older adults, the pathophysiological mechanisms underlying LUTS onset and progression are not fully understood.

Central sensitization (CS) is proposed as a mechanism of LUTS (8). CS occurs when the central nervous system amplifies noxious sensory signals resulting in hypersensitivity to painful stimuli (9). Features of CS have been identified in almost all chronic pain conditions, including painful urinary conditions such as bladder pain syndrome and chronic prostatitis. What is unknown is whether CS also might contribute to a portion of nonpainful LUTS cases or to LUTS progression. CS generally results in the amplification of painful stimuli and may increase the degree to which pain interferes with an individual's ability to engage in physical, social, emotional, or cognitive activities. However, many people with CS also exhibit hypersensitivity to nonpainful stimuli such as sound, light, and odor (9). Specifically, it has been proposed that the sensory amplification of bladder stretch or pressure may be translated into storage LUTS, such as urinary urgency, frequency, and nocturia (8).

Chronic conditions that exhibit features of CS, such as fibromyalgia and low back pain, tend to co-occur (9,10). The term chronic overlapping pain conditions (COPCs) is used to describe the comorbid nature of these conditions and to indicate that CS likely plays a prominent role in their pathogenesis (11). The co-occurrence of COPCs and painful urinary conditions like bladder pain syndrome has been documented (12,13). Emerging evidence demonstrates overlap in the prevalence of COPCs, or symptoms suggestive of CS/COPCs, and nonpainful LUTS (14–17), although the majority of these studies were conducted in women. Recently, we showed that the prevalence of musculoskeletal pain is greater among community-dwelling men with moderate or severe LUTS compared with those with no/mild LUTS (18). Furthermore, there was a strong positive association with multilocation pain and LUTS severity. Together, these findings suggest that CS may be associated with the presence of LUTS, but whether CS is associated with LUTS progression remains an unanswered question.

Building on our initial work using musculoskeletal pain as a possible indicator of CS, the objective of this study was to investigate whether musculoskeletal pain may be a risk factor for LUTS progression among community-dwelling men. We hypothesized that men who reported musculoskeletal pain and those with higher levels of pain interference would be more likely to experience worsening LUTS over time compared with men without pain.

Method

Data Source

The Osteoporotic Fractures in Men (MrOS) study is a multicenter, prospective cohort study designed to identify risk factors for fracture and other conditions of aging in men (19). After identification through population-based lists (eg, motor vehicle and voting registries), eligible individuals were recruited through mass mailings (20). Participants were enrolled at 6 academic medical centers in Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland (OR), and San Diego. Between March 2000 and April 2002, 5 994 community-dwelling men who were at least 65 years old and could walk without the assistance of another person were enrolled in MrOS. At baseline, all men completed a comprehensive self-administered questionnaire and an in-person study visit. The questionnaire was repeated approximately 2 (July 2002–March 2004) and 4 (March 2005–May 2006) years after each participant's baseline enrollment date. All participants gave written informed consent, and Institutional Review Boards at each participating institution approved the study.

Exposure Variables: Musculoskeletal Pain

We defined 3 primary exposure variables for this study: any musculoskeletal pain, multilocation pain, and pain interference. In separate questions on the baseline assessment, MrOS participants reported whether they had any back, neck, hip, or knee pain within the previous 12 months. We defined any musculoskeletal pain as a response of "yes" to any of the 4 pain locations versus "no" for all locations. Multilocation pain was defined as the sum of the number of "yes" responses to the 4 individual questions about back, neck, hip, or knee pain (0, 1, ≥ 2). Pain interference was assessed with the following question from the SF-12 questionnaire (21): "During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?" Possible responses included "not at all," "a little bit," "moderately," "quite a bit," or "extremely." To attain a category with a sufficient number of participants for analysis, we combined men who responded "quite a bit" (n = 328) and "extremely" (n = 63) into one category.

Other Independent Variables

Race was categorized as White, Black, or other because there were too few men to examine other racial and ethnic categories separately. Education was categorized as college degree (yes/no). Study site was categorized as one of the 6 academic medical center recruitment sites. Height and weight were measured at the in-person baseline study visit using calibrated scales and a stadiometer (19) and used to calculate a standard body mass index (BMI). BMI was assessed as categories of normal (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2). Cigarette smoking status was categorized as current, former, or never. Current alcohol consumption was assessed as average intake in a typical week and categorized as none, 1–7, and >7 drinks per week. Problem drinking was defined as a score of ≥2 on the CAGE Substance Abuse Screening Tool (19). Physical activity was assessed with the Physical Activity Scale for the Elderly (19); scores were categorized into quartiles. Mobility limitation was defined as self-report of any difficulty walking 2–3 blocks outside on level ground or any difficulty climbing 10 steps without resting. Prescription medication use was derived from labels on products brought to the study visits by participants. Product information was entered into an electronic medications inventory (San Francisco Coordinating Center, San Francisco, CA). Each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA) (22). For this study, LUTS medications were assessed as current use of any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor, anticholinergic, or phosphodiesterase-5 inhibitor. Pain medications were assessed as current use of nonsteroidal anti-inflammatory drugs,

opioids, acetaminophen, or aspirin. Current antidepressant or anxiolytic medication use was coded as a binary variable indicating use of selective serotonin receptor inhibitors, serotonin-norepinephrine reuptake inhibitors, tri/tetracyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, barbiturates, or pharmaceuticals indicated for treatment of depression or anxiety that do not belong to one of these categories (eg, trazodone, buspirone). Men with missing antidepressant or anxiolytic medication information (n = 239) were coded as nonusers because results with this coding were similar to results excluding the missing observations. We also assessed the use of diuretics. Self-report of physician-diagnosed hypertension, diabetes, prostatitis, and prostate cancer were also obtained. A multimorbidity score was defined as the number of physician-diagnosed chronic conditions, including angina, myocardial infarction, heart failure, stroke, chronic obstructive pulmonary disease, diabetes mellitus, Parkinson's disease, osteoporosis, osteoarthritis, hyperthyroidism, or hypothyroidism (23). Self-report history of prostate surgery was categorized as yes/no. We defined psychological distress as a score of ≤50 on the mental health component of the SF-12 questionnaire (which does not include the pain interference question) (24).

Outcome Variable: Incident LUTS Progression

LUTS were assessed with the American Urologic Association Symptom Index (AUA-SI) at baseline and 2 and 4 years of follow-up. The AUA-SI includes 7 items on urinary urgency, frequency, nocturia, straining, weak stream, intermittency, and/or incomplete emptying in the previous 30 days. Items were summed for a total score of 0–35 points, and LUTS were categorized as no/mild (0–7 points), moderate (8–19 points), or severe (≥20 points) according to standard practice (25). A 3- to 4-point change on the AUA-SI is generally accepted as a clinically relevant change in LUTS (26). We defined incident LUTS progression as a ≥4-point increase from the previous score such that the current AUA-SI score was at least 8 points. Men who did not experience LUTS progression at the 2-year follow-up remained at risk for incident LUTS progression at the 4-year follow-up assessment.

Men who withdrew from the study, were lost, or died prior to completing a follow-up assessment could not be observed for LUTS progression. For men who remained enrolled in the study, ascertainment of LUTS progression was over 98% complete at each follow-up assessment.

Analytic Cohort

Of the 5 994 MrOS participants, men with missing data for LUTS severity (n = 4) and other independent variables of interest (n = 23) were excluded. Men with severe LUTS at baseline (AUA-SI ≥ 20; n = 398) were also excluded because of a potential ceiling effect with the AUA-SI and symptom progression may represent a different physiologic process for them compared with men who progress from mild or moderate LUTS. The analytic sample consisted of 5 569 men. Each participant contributed follow-up time from baseline until LUTS progression, date of death, withdrawal, last known contact, or the 4-year follow-up assessment occurred, whichever came first.

Statistical Analysis

We compared characteristics of the analytic cohort according to any musculoskeletal pain status using 1-way analysis of variance (ANOVA) for continuous variables or chi-square tests of independence for categorical variables. We also computed the unadjusted prevalence of pain interference among those with any musculoskeletal pain, pain at one location, and pain at ≥2 locations.

To estimate the association between musculoskeletal pain and LUTS progression, we used multivariable pooled logistic regression for grouped failure times (27) and a sandwich variance estimator. We used this established pooled method because the exact date of each participant's LUTS progression was unknown. We then used output from the pooled logistic regression to estimate the adjusted incidence rate of LUTS progression (28). Specifically, the incident rate of LUTS progression for each category of musculoskeletal pain can be calculated by dividing the pooled number of LUTS progression events by the pooled person-years at risk in each pain category. The IRR is then calculated as the incidence rate in the pain category of interest divided by the incidence rate for the reference category of no musculoskeletal pain.

We hypothesize that musculoskeletal pain, as a proxy for CS, is associated with LUTS progression. If true, musculoskeletal pain and LUTS progression would be associated through a common cause, CS, that was not measured in this study. Therefore, we created a conceptual framework to guide our analysis (Supplementary Table) (29). We adjusted for factors that confounded the association between musculoskeletal pain and LUTS progression *independent* of CS using a change in estimate approach (30). All base models were adjusted for age. Additional covariables were selected in a series of iterative and systematic steps (30), First, we specified 4 groups of candidate confounders: demographics (race, education), health behaviors (smoking status, alcohol consumption, physical activity), health status (mobility limitation, BMI, diabetes, hypertension, prostate cancer, prostate surgery), and medications (diuretics). We constructed a full multivariable model adjusted for age and all 4-candidate confounder groupings. Then, we removed each candidate grouping from the full model one at a time and calculated the percentage change in the IRR for each musculoskeletal pain category. Any group that resulted in ≥10% change in the measures of association was retained in the model. We then followed a similar process to determine which individual variables confounded the measure of association. Specifically, for every confounder grouping retained in the model, each variable within the group was removed from the model one at a time. If the change in the measures of association was <1%, the variable was permanently removed. This step was repeated until each group contained only variables that confounded the final measure of association. As a result of these procedures, age, history of prostate surgery, hypertension, multimorbidity, and mobility difficulties were retained in the final model.

Additional factors, including pain medication use, LUTS medication use, psychological distress, and prostatitis, may lie on the causal pathway between CS and pain or CS and LUTS progression (Figure 1). To assess the impact of further adjusting for these factors, we created a second multivariable model. We added the 4 variables to the final model simultaneously. We then removed each variable one at a time and retained only those whose removal resulted in ≥1% change in the

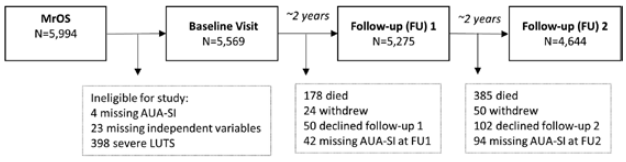

Figure 1. Timeline of follow-up assessments in the MrOS study. *N* at each study assessment represents number of participants with complete assessments for musculoskeletal pain and LUTS. AUA-SI, American Urological Association Symptom Index; FU, follow-up; LUTS, lower urinary tract symptoms.

measure of association. As a result, age, history of prostate surgery, hypertension, multimorbidity, mobility difficulties, prostatitis, psychological distress, and LUTS medication use were retained in this second model. We updated baseline values with responses from the 2-year assessment to account for changes during follow-up in smoking status, drinks per week of alcohol, history of prostate surgery, history of prostatitis, and LUTS medication status.

We anticipated that the loss of data from men who were censored (those who died, withdrew, or were lost to follow-up) during the observation period might induce selection bias in our analytic sample. Therefore, we used inverse probability of censoring weighting to assign extra weight to men who were not censored yet had similar covariate patterns to those who were censored. We used logistic regression to calculate the cumulative probability of censoring in each follow-up interval as a function of covariate and exposure status (31). We then applied stabilized weights to each noncensored observation and repeated our analyses (31). A p-value of ≤.05 was considered significant for all statistical tests; Stata 14.2 (StataCorp LLC, College Station, TX) was used for all analyses.

Sensitivity Analysis

Our primary analysis estimates the incidence of LUTS progression over a 2-year period, and thus may miss men whose symptoms progress more slowly over a longer period of time. Therefore, we also assessed whether musculoskeletal pain is associated with LUTS progression over 4 years. Specifically, for this analysis, incident LUTS progression was evaluated at the 4-year follow-up assessment and was defined as a ≥4-point increase because the baseline AUA-SI measurement such that the 4-year follow-up AUA-SI score was at least 8 points.

Results

The majority of men (81%) reported musculoskeletal pain at baseline (Table 1). Compared with men without pain, those with any musculoskeletal pain were proportionally less likely to have a college degree, more likely to be obese, report mobility limitations, and to use medications for pain and LUTS. Men with musculoskeletal pain were also more likely to report hypertension, prostatitis, a history of prostate surgery, psychological distress, and had higher mean multimorbidity scores than men who did not report pain.

Among men with any musculoskeletal pain, nearly half (47%) reported no pain interference, 30% reported a little interference, and 23% reported at least moderate pain interference (Table 2). Among men with pain at one location, 64% reported no pain interference and 12% reported at least moderate interference. In comparison, men with pain at 2 or more locations were less likely to report no interference (36%) and more likely to report at least moderate interference (30%).

In total, 1 838 men experienced LUTS progression over 17 936 observed person-years at risk (Table 3). Musculoskeletal pain was positively associated with LUTS progression. After adjusting for potential confounders, the incidence rate of LUTS progression was 37% higher among men with any musculoskeletal pain compared with men with no pain (IRR 1.37, 95% confidence interval [CI]: 1.21, 1.54). The association of musculoskeletal pain at one and ≥2 locations with LUTS progression was of a similar magnitude and direction (1 location: IRR 1.31, 95% CI: 1.13, 1.48; ≥2 locations: IRR 1.42, 95% CI: 1.24, 1.60). The incidence of LUTS progression rose with increasing levels of pain interference. Men with quite a bit/extreme pain interference were the most likely to experience LUTS progression compared with men with no pain (IRR 1.47, 95% CI: 1.22, 1.71). Further adjustment for history of prostatitis, psychological distress, and LUTS medication use did not materially change these results.

The odds ratios and 95% CI for these associations estimated after the application of stabilized weights (Supplementary Table) were nearly identical to the estimates reported in Table 3.

Sensitivity Analysis

Among men who completed the 4-year follow-up, those with any pain were 42% more likely to experience LUTS progression over 4 years compared with men with no pain (adjusted cumulative incidence ratio [CIR]: 1.42, 95% CI: 1.20, 1.65), as were men with pain at 1 and 2 or more locations (CIR 1.30, 95% CI: 1.07, 1.52; CIR 1.52, 95% CI: 1.27, 1.76, respectively). Similar to our primary analyses, men with quite a bit/extreme pain interference were the most likely to experience LUTS progression compared with men with no pain (CIR 1.39, 95% CI: 1.09, 1.69).

Discussion

In this large U.S. cohort of community-dwelling older men, individuals with musculoskeletal pain had an increased rate of LUTS progression over 2 years, independent of age, prostatitis, prostate surgery, hypertension, mobility difficulties, psychological distress, and LUTS medication use. The association between musculoskeletal pain and LUTS progression was similar among men with pain at 1 and 2 or more bodily locations. The rate of LUTS progression rose with increasing levels of pain interference and was highest for those with at least moderate pain interference. Our results lend further support to the hypothesis that musculoskeletal pain is a risk factor for progression of nonpainful LUTS in older community-dwelling men, perhaps via CS mechanisms.

There is some prior evidence of a positive association between musculoskeletal pain and LUTS progression. Two prospective studies suggest an association between incident back pain and urinary incontinence in older women (mean age 72.5 [*SD* 1.5] years) (32,33). In older men, those with progressing LUTS trajectories were more likely to have back pain compared with those with stable trajectories (34). Our observation that musculoskeletal pain is associated with LUTS progression is consistent with these earlier findings and extends these works by assessing pain at multiple locations as well as pain interference. The consistency in associations we observed between musculoskeletal pain outcomes of any pain, multilocation pain, and pain interference and LUTS progression further strengthens the evidence in support of this relationship.

While CS is generally conceptualized as a mechanism of chronic pain, there are several ways in which it could contribute to LUTS. In general, repeated, noxious sensory stimuli and/or tissue damage can increase afferent nervous system signaling above normal thresholds resulting in a state of elevated central nervous system reactivity, or CS (8). In the urinary tract specifically, mechanical or chemical trauma, repeated infections, ongoing changes in local pH, and immune-mediated inflammation can compromise urothelial tissues (35,36). It is hypothesized that the increased afferent signaling from chronic insults such as these could cause CS, resulting in abnormalities in lower urinary tract sensation and function (35).

Because CS mechanisms are located in the central nervous system, the effects of CS are not limited to the anatomic location in which

Table 1. Baseline Characteristics of Community-Dwelling Men Aged ≥ 65 y by Musculoskeletal Pain Status Within the Previous 12 mo: The Osteoporotic Fractures in Men Study, United States

	No Pain	Any Pain	
	n (%)	*n* (%)	*p* Value*
N (% in cohort)	1 064 (19.1)	4 505 (80.9)	
Age, y; mean (*SD*)	73.71 (5.76)	73.54 (5.85)	.39
Race			.16
American Indian/Alaskan Native	1 (0.1%)	5 (0.1%)	
Asian	53 (5.0%)	128 (2.8%)	
Black	37 (3.5%)	178 (4.0%)	
Hawaiian/Pacific Islander	2 (0.2%)	4 (0.1%)	
White	949 (89.2%)	4 063 (90.2%)	
More than one race	7 (0.7%)	48 (1.1%)	
Unknown	15 (1.4%)	79 (1.8%)	
College degree	619 (58.2%)	2 355 (52.3%)	<.001
Body mass index			<.001
Under/normal (<25.0 kg/m^2)	347 (32.6%)	1 190 (26.4%)	
Overweight (25.0-29.9 kg/m^2)	543 (51.0%)	2 310 (51.3%)	
Obese (≥30 kg/m^2)	174 (16.4%)	1 005 (22.3%)	
Smoking status			.01
Never	448 (42.1%)	1 655 (36.7%)	
Past	580 (54.5%)	2 695 (59.8%)	
Current	36 (3.4%)	155 (3.4%)	
Alcohol consumption†			.82
None	383 (36.0%)	1 575 (35.0%)	
1-7 drinks/wk	367 (34.5%)	1 578 (35.0%)	
>7 drinks/wk	314 (29.5%)	1 352 (30.0%)	
Problem drinking	155 (14.6%)	764 (17.0%)	.06
Physical activity quartiles‡			.37
Q1 (least active)	274 (25.8%)	1 124 (25.0%)	
Q2	244 (22.9%)	1 144 (25.4%)	
Q3	267 (25.1%)	1 125 (25.0%)	
Q4 (most active)	279 (26.2%)	1 112 (24.7%)	
Mobility limitations§	47 (4.4%)	682 (15.1%)	<.001
Medication use			
Pain medications‖	384 (36.1%)	2 202 (48.9%)	<.001
LUTS medications¶	144 (13.5%)	867 (19.2%)	<.001
Diuretic medications	170 (16.0%)	868 (19.3%)	.01
Antidepressant/anxiolytic medications#	52 (4.9%)	411 (9.1%)	<.001
Medical history			
Diabetes	114 (10.7%)	476 (10.6%)	.89
Hypertension	378 (35.5%)	1 990 (44.2%)	<.001
Prostatitis	191 (18.0%)	1 131 (25.1%)	<.001
Prostate cancer	107 (10.1%)	544 (12.1%)	.07
Prostate surgery	152 (14.3%)	827 (18.4%)	.002
Multimorbidity; mean (*SD*)**	0.66 (0.89)	0.96 (1.10)	<.001
Psychological distress††	100 (9.4%)	776 (17.2%)	<.001

Notes: MrOS = Osteoporotic Fractures in Men Study; PASE = Physical Activity Scale for the Elderly.

**p*-Values estimated from a chi-square test for categorical variables or one-way analysis of variance for continuous variables.

†Defined as a score of ≥2 on the CAGE Substance Abuse Screening Tool.

‡Physical activity assessed with the Physical Activity Scale for the Elderly.

§Defined as any difficulty walking 2–3 blocks or climbing 10 steps.

‖Use of nonsteroidal anti-inflammatory drugs, opioids, acetaminophen, or aspirin.

¶Use of any alpha-1 adrenergic antagonist, 5-alpha reductase inhibitor., anticholinergic for storage symptoms, or phosphodiesterase-5 inhibitor.

#Use of selective serotonin receptor inhibitors, serotonin-norepinephrine reuptake Inhibitors, tri/tetracyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, barbiturates, or pharmaceuticals indicated for treatment of depression or anxiety that do not belong to one of these categories (eg, trazodone, buspirone).

**Mean number of the following physician-diagnosed conditions: thyroid disease, diabetes, angina, myocardial infarction, congestive heart failure, stroke, chronic obstructive pulmonary disease, Parkinson's disease, osteoarthritis, and osteoporosis.

††Defined as a mental health component score of ≤50 on the SF-12.

symptoms present. For example, compared with healthy controls, individuals with painful urinary conditions exhibit hypersensitivity to pain on laboratory bladder filling (37) as well as decreased pain tolerance to nonpelvic mechanical and thermal stimuli (38–40). Studies suggest that women with overactive bladder also exhibit similar findings (41,42). Together these results suggest that features of CS are associated with

Table 2. Pain Interference in Community-Dwelling Men Aged ≥ 65 y According to Musculoskeletal Pain Status Within the Previous 12 mo: The Osteoporotic Fractures in Men Study, United States

		Pain Interference			
		None	A little	Moderate	Quite a bit/extreme
	n	*n* (%)	*n* (%)	*n* (%)	*n* (%)
No musculoskeletal pain	1 064	909 (85.4)	121 (11.4)	22 (2.1)	12 (1.1)
Any musculoskeletal pain	4 505	2 113 (46.9)	1 355 (30.1)	658 (14.6)	379 (8.4)
Pain at 1 location	1 793	1 142 (63.7)	439 (24.5)	153 (8.5)	59 (3.3)
Pain at ≥ 2 locations	2 712	971 (35.8)	916 (33.8)	505 (18.6)	320 (11.8)

Table 3. Association Between Musculoskeletal Pain and the Progression of Lower Urinary Tract Symptoms (LUTS) Over 2 y Among Community-Dwelling Men aged ≥65 y : The Osteoporotic Fractures in Men Study, United States

	LUTS Progression					
	n	Person-Years of Follow-up	No. Progressed	Age-Adjusted IRR (95% CI)	Multivariable* IRR (95% CI)	Multivariable† IRR (95% CI)
Any Pain						
No pain	1 064	3 580	272	Ref.	Ref.	Ref.
Any pain	4 505	14 356	1 566	1.45 (1.27, 1.62)	1.37 (1.21, 1.54)	1.33 (1.17, 1.49)
Multilocation pain						
No pain	1 064	3 580	272	Ref.	Ref.	Ref.
Pain at one location	1 793	5 768	579	1.33 (1.15, 1.51)	1.31 (1.13, 1.48)	1.28 (1.11, 1.45)
Pain at ≥ 2 locations	2 712	8 588	987	1.52 (1.33, 1.71)	1.42 (1.24, 1.60)	1.37 (1.19, 1.54)
Pain interference						
No interference	3 022	9 992	900	Ref.	Ref.	Ref.
A little interference	1 476	4 766	510	1.19 (1.07, 1.30)	1.15 (1.03, 1.26)	1.14 (1.02, 1.25)
Moderate interference	680	2 068	257	1.38 (1.21, 1.55)	1.28 (1.11, 1.45)	1.24 (1.08, 1.41)
Quite a bit/extreme interference	391	1 110	171	1.67 (1.43, 1.91)	1.47 (1.22, 1.71)	1.40 (1.16, 1.64)

Notes: AUA-SI = American Urological Association Symptom Index; IRR = incidence rate ratio; CI = confidence interval.

*Adjusted for age, hypertension, multimorbidity, mobility difficulties, and history of prostate surgery.

†Adjusted for age, hypertension, multimorbidity, mobility difficulties, history of prostate surgery, history of prostatitis, psychological distress, and LUTS medication use.

the presence of painful and nonpainful urinary symptoms. Evidence from COPC studies also suggests that CS may contribute to symptom progression. CS is implicated in the progression of episodic to chronic migraine (43) and tension type headaches (44). Additionally, having one COPC may increase the risk of developing future COPCs (45). Thus, the presence of CS might contribute not only to the worsening of a singular condition such as LUTS, but could also promote the onset and progression of nonurological symptoms in which CS plays a role.

The majority of current medications for male LUTS have pharmacologic mechanisms that target the prostate or bladder and are limited by side effects, modest efficacy, and the need for chronic therapy (7). If CS contributes to a subset of progressive LUTS cases, these individuals may benefit from interventions that also target the nervous system. For example, repetitive transcranial magnetic stimulation (rTMS) is a noninvasive intervention that stimulates cortical neurons and, over time, can result in structural and functional synaptic changes (46). Clinically, rTMS is used to treat pain conditions and it has been hypothesized that some analgesic effects of rTMS may be derived by acting on CS mechanisms (47). Emerging evidence suggests that rTMS applied to cortical areas associated with the pelvic region may improve LUT function as well as voiding and storage symptoms in people with multiple sclerosis, Parkinson's disease, and bladder pain syndrome (48). Mind–body interventions such as mindfulness training can also alter neural circuits related to the integration of pain and other sensory signals (49). Although we are aware of only small mindfulness-based interventions that have been piloted for women with urge incontinence (50,51), the approach has improved symptoms in other conditions with a CS component and could hold promise for LUTS in older men.

Our study has limitations. First, although a validated measure of CS symptoms now exists (10), it was not yet developed at the time the MrOS cohort was assembled so we used musculoskeletal pain as a proxy for CS. Nevertheless, musculoskeletal pain in multiple locations is a marker of disordered central pain regulation making it a suitable surrogate for the presence of CS (9). Furthermore, as a measure of emotional reactivity to pain, pain interference may be a better indication of CS than the number of locations in which pain occurred (52). Second, CS is thought to be more likely a mechanism of chronic rather than acute pain and we were unable to differentiate chronic from acute pain in these analyses. We have no reason to believe that the reporting of acute pain would be systematically different among men whose LUTS subsequently progressed and those whose LUTS did not; therefore, the inclusion of acute pain in our analyses could have resulted in an underestimation of IRRs. Third, pain status and pain interference included different recall periods (1 year and 4 weeks, respectively) and we do not know if pain interference was a result of musculoskeletal

pain or other pain mechanisms. Fourth, we lacked a measure of lower urinary tract pain and therefore were unable to determine whether the association between musculoskeletal pain and LUTS progression exists among men with painful urinary conditions and nonpainful LUTS, although we were able to adjust for prostatitis—a condition that often causes pelvic pain and dysuria. Fifth, LUTS fluctuate over time, complicating the measurement of symptom change over prolonged periods. Nevertheless, we observed consistent results when assessing change over 2- and 4-year intervals, suggesting our definition was a reasonable measure of LUTS progression. Sixth, the observed association may be confounded by factors that were unmeasured and therefore could not be controlled for in analyses. In the future, it would be useful to assess factors that may influence both pain and LUTS progression, including resilience or coping mechanisms. Seventh, the MrOS cohort comprised mostly White participants. Our measure of association may not generalize to more diverse study samples as racism and discrimination are known to affect pain reporting, access to care, and pain management. Finally, MrOS is a cohort of older men, and some inevitably died during the observation period. Our sensitivity analysis, however, suggests that deaths in the follow-up interval did not affect our findings.

Conclusion

The presence of musculoskeletal pain and the extent to which it interferes with daily activities is associated with worsening LUTS among older men. Musculoskeletal pain and LUTS may share an underlying mechanism, CS. Studies that investigate whether the validated presence of CS is associated with LUTS progression among older men are warranted. If future studies identify CS as a risk factor for LUTS progression, then opportunities for new nonpharmacologic treatment targets for individuals with specific LUTS phenotypes or those who do not respond to current LUTS interventions may arise.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

Author Contributions

A.S.: conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval of the version to be published. S.R.B.: conception and design, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. Y.C.: conception and design, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. B.O.: conception and design, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. H.A.F.: conception and design, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. N.E.L.: conception and design, revising the article for important intellectual content, final approval of the version to be published. K.P.S.: conception and design, revising the article for important intellectual content, final approval of the version to be published. L.M.M.: conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval of the version to be published.

Data Availability

Data used in this project is publicly available at https://mrosonline.ucsf.edu/.

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