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Movement Impairments in Women with and without Urinary Urgency/Frequency

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Abstract

Objectives: 1) examine the relationship between spine, hip, and pelvis movement patterns and urinary urgency and frequency 2) report the prevalence of pelvic girdle and hip joint impairments among women with and without urinary urgency and frequency 3) report the most common movement impairments observed in women with and without urinary urgency and frequency.

Methods: Women age 18–60 with urinary urgency and frequency were matched 1:1 to women without on age, body mass index, and vaginal parity. Participants completed primary movement tests of the hip, pelvis and spine. Additional clinical tests included Stork test, sidelying position, pubic symphysis palpation, flexion-abduction-external rotation, flexion-adduction-internal rotation, and seated hip internal and external rotation. Urge symptoms were monitored before and during each test. Movement patterns and positioning of the thoracic and lumbar spine, pelvis, and hips were observed. Secondary tests to correct a movement or positional impairment were performed if an impairment was noted or if symptoms were provoked during the primary test.

Results: 42 women completed testing. More participants with urinary urgency and frequency 1) demonstrated impairments during forward bend, single leg stance, sidelying and Stork tests; 2) reported urgency provocation during forward bend, flexion-adduction-internal rotation test, pubic symphysis palpation, and hip internal rotation; and 3) reported symptom relief with sidelying position secondary test; and secondary tests of the thoracic, lumbar and hip regions compared to those without.

Conclusion: Musculoskeletal impairments may be associated with urinary urgency and frequency and should therefore be considered when determining management options for these patients.

Keywords

Urinary Bladder, Overactive; Lower Urinary Tract Symptoms; Musculoskeletal system; Movement; Physical Therapy Specialty

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Introduction

Urinary urgency and frequency are two of the most common lower urinary tract symptoms (LUTS) experienced by women.[1] Urinary urgency is the sudden compelling desire to pass urine which is difficult to defer and is often accompanied by urinary frequency, the complaint that micturition occurs more frequently during waking hours than previously deemed normal by the woman.[2] Medical management for urgency and frequency predominant LUTS (UFLUTS) is multifactorial and often requires trials of different strategies to identify what is most effective for each patient.[3] Physical therapy is one treatment option for patients with UFLUTS and traditionally consists of pelvic floor targeted therapy to address pelvic floor impairments through strengthening and muscle coordination training.[4–7] In addition to treating pelvic floor impairments, physical therapy can also address other musculoskeletal impairments that may be associated with UFLUTS.[8–13]

Musculoskeletal impairments of the low back, hip, and pelvic floor muscles have been shown to be associated with LUTS and therefore may also be associated with UFLUTS.[8–13] Differences in hip range of motion and strength have been reported in patients with and without urinary incontinence.[12] Anterior hip surgical techniques have been reported to result in lower incidence of urinary incontinence after surgery compared to posterior surgical techniques.[9] This may be due to sparing the obturator internus and its fascial connections to the pelvic floor musculature with anterior surgical approaches. Patients with LUTS and low back pain have reported improvements in urinary symptoms with physical therapy interventions targeting the low back.[11] Patients with LUTS have also been reported to have increased sagittal spinal curvature, increased spine mobility, and greater presence of low back pain compared to patients without LUTS.[10] These suggest physical examination of patients presenting with LUTS should not be limited to the assessment of pelvic floor musculature. This literature, however, has been mostly focused on patients with urinary incontinence. It is logical that similar musculoskeletal impairments are present for patients with UFLUTS.

Given the potential relationship between musculoskeletal impairments and UFLUTS, we developed a systematic examination to assess the relationship between movement and UFLUTS. The examination is based on the movement system impairment (MSI) approach which is a systematic musculoskeletal examination that has been previously described for diagnosing and treating musculoskeletal pain conditions.[14] The physical therapist identifies specific movements and positions that aggravate or ease a patient's symptoms and guides the patient to change their movement and positions to reduce symptoms during activities of daily living. Although the MSI approach was originally developed to assess pain conditions, we modified the approach to assess the relationship between movement impairments and UFLUTS. In our retrospective analysis of our systematic examination evaluating the relationship between movement and UFLUTS on patients presenting to physical therapy for treatment of UFLUTS, we noted musculoskeletal impairments of the hip and spine that provoked UFLUTS. [8]

The purpose of this study was to prospectively assess the relationship between musculoskeletal impairments and UFLUTS using our systematic examination and additional

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clinical tests. The objectives of the current study were to 1) examine the relationship between spine, hip, and pelvis movement patterns and UFLUTS 2) report the prevalence of pelvic girdle and hip joint impairments among women with UFLUTS compared to women without and 3) report the most common movement impairments observed in women with UFLUTS compared to women without. We hypothesized 1) more participants with UFLUTS than without would demonstrate movement impairments 2) more participants with UFLUTS would present with pelvic girdle and hip joint impairments compared to those without 3) urge provocation with movement and additional clinical tests would occur in those with UFLUTS compared to those without and 4) UFLUTS would be relieved with movement pattern correction.

Materials and Methods

Study Design

The study was a cross-sectional examination of women with and without UFLUTS. The study was approved by the Human Research Protection Office of [INSTITUTION REDACTED FOR REVIEW] (approval #201810086) and conducted in accordance with Declaration of Helsinki. Participants were fully informed about the nature and purpose of the study. Participants provided written informed consent prior to participation.

Study Population

Participants in this exploratory analysis were recruited as part of a case-control study examining pelvic floor and hip muscle strength in UFLUTS.[15] In April to December 2019, female participants age 18–60 with and without UFLUTS were recruited from the community via paper and social media advertisements, emails, research recruitment fairs, and a research participant registry. Participants with UFLUTS were included if they experienced bothersome urgency and/or day/night frequency at least sometimes in the past 4 weeks. Participants with UFLUTS were matched 1:1 to participants without (control) based on age, body mass index (BMI) and vaginal parity. It was determined a priori that +/− 5 year age or +/− 5 kg/m^2 BMI was appropriate 1:1 matching criteria for the aims of the parent study. Potential participants were excluded if they reported stress or mixed urinary incontinence more than once per month. Participants with self-reported or positive screen for urinary tract infection or pelvic organ prolapse were also excluded. Full inclusion and exclusion criteria are described in Table 1.

UFLUTS and activity assessment

Study data were collected and managed using REDCap electronic data capture tools.[16] Prior to examination, participants completed web-based questionnaires including the LUTS Tool[17] for a comprehensive assessment of participants' LUTS, the Pelvic Floor Impact Questionnaire short form (PFIQ-7)[18] for a general overview of impact of symptoms on daily activities and quality of life, and the UCLA Activity Score[19] for a general overview of activity and exercise level.

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Final Eligibility Exam

To determine final eligibility, a urine screen and a pelvic organ prolapse screen was completed. Using 10SG and human chorionic gonadotropin (HCG) test strips (McKesson, Irving, TX, USA), participants were excluded if their urine tested positive for glucose, nitrite, blood, leukocyte esterase, or HCG. After urine screening, a transabdominal ultrasound scan was performed to confirm whether the bladder was empty (Clarius C3 curvilinear scanner, Clarius Mobile Health Corp, Burnaby BC). If postvoid residual urine was evident, participants were asked to void again prior to intravaginal exam. A pelvic organ prolapse screen was performed with the participant supine with knees bent and feet flat on the exam table. A lubricated sterile wide tongue depressor was used to retract the vaginal wall as the participant bore down. Participants were excluded if any intravaginal landmark descended beyond the vaginal introitus (hymenal ring). [1,2] The final eligibility items and clinical examination were performed by a single assessor, a physical therapist who has postgraduate training in pelvic health (Herman and Wallace Pelvic Rehabilitation Practitioner Certification) and fellowship training in movement assessments.

Clinical Examination

Prior to each test, participants were asked to rate their baseline sensation of bladder urgency on a scale from 0–4 with 0 indicating no bladder sensation and 4 indicating an urgent desire to void where voiding cannot be delayed for more than 5 minutes.[20] During each test, participants were asked to report 1) whether their bladder urgency got better, worse, or stayed the same compared to their baseline urgency symptoms, and 2) if they experienced pain.

The examiner instructed participants to perform movement and position tests under two conditions. For the first condition (primary test) participants were asked to perform the task using their preferred strategy.[21] Primary tests were conducted for movements that mimic activities of daily living including: forward bend, return from forward bend, single-leg stance, and sidelying. A description of these tests is included in Table 2. The examiner observed the performance of the primary test, and participants were asked to report if their urgency symptoms were worse, better, or the same compared to baseline. The examiner documented the participant's preferred movement pattern as well as the position of the thoracic and lumbar spine, pelvis, and hips during each primary test. A movement/positional impairment was defined as alignment or movement performance that deviates from an ideal kinesiological standard.[14] Movement tests were conducted under the second condition (secondary test) if urgency symptoms stayed the same or became worse during the primary test (urgency provoked), or if movement or positional impairments were identified during the primary test. Secondary tests consisted of standardized modifications to the primary test by modifying the way the participant moves or aligns the spine, hips or pelvis during the task.[21] A description of common movement impairments and secondary tests is included in Appendix 1. A list of all movement impairments observed are presented in Appendix 2. During the secondary test, participants were asked if their urgency symptoms were worse, better, or the same compared to their symptoms during the primary test. Urgency relieved was counted if the participant reported reduced bladder urgency during the secondary test when compared to their symptoms during the primary test.

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Additional Clinical Tests

To assess pelvic girdle and hip joint involvement, the examiner performed additional clinical tests including the Stork test,[22] seated passive hip internal (IR) and external rotation (ER), hip flexion-abduction-external rotation test (FABER),[23] and hip flexion-adduction-internal rotation test (FADIR).[23] A description of these tests is included in Table 2. Criteria for determining a positive test are described in Table 3. Urgency symptoms were monitored during the FABER, FADIR, hip range of motion (ROM), and pubic symphysis palpation tests. Secondary tests were not conducted for the additional clinical tests.

Statistical Analysis

Descriptive statistics were computed for participant characteristics and questionnaire scores. Baseline demographics were compared between groups using paired sample t-tests or Wilcoxon signed rank tests.[24] Frequency distributions were calculated for all categorical data. Data analyses were performed using IBM SPSS Statistics (version 25 IBM Corporation, Armonk, NY) and Microsoft Excel (Microsoft Excel Version 16 (Microsoft, Redmond WA). Fisher's exact analyses were conducted to test for between group differences in number of participants who demonstrated movement and positional impairments, positive additional clinical tests, and provocation of urgency symptoms with primary and additional clinical tests.

Results

Participant Characteristics

Forty-two women were enrolled, 21 with UFLUTS and 21 control participants without UFLUTS. Descriptive characteristics of study participants are presented in Table 4.

Observed Movement and Positional Impairments and Positive Additional Clinical Tests

More participants with UFLUTS demonstrated movement impairments during return from forward bend (P=.03), single leg stance (P<.01), and sidelying (P<.01) primary tests compared to the control group. More participants in the UFLUTS group demonstrated a positive Stork test determined by cephalad motion of the posterior superior iliac spine relative to the sacrum during single leg stance (P<.01) compared to the control group (Table 5).

Urgency Provocation during Primary Tests and Additional Clinical Tests

Of the 21 participants with UFLUTS, 8 reported symptom provocation during at least one primary tests. More participants with UFLUTS reported worse urgency during return from forward bend (P<.05), FADIR (P=.02), pubic symphysis palpation (P<.01), and hip IR ROM (P<.01) tests compared to the control group (Table 5).

Urgency Relief during Secondary Tests

Of the 21 participants with UFLUTS, 12 reported relief of symptoms with secondary tests. Participants with UFLUTS most commonly reported relief of urgency symptoms during the secondary test performed in sidelying (n=11 with UFLUTS) (Table 5). Relief

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of urgency during secondary tests occurred when correcting impairments of the hip (n=11 with UFLUTS), thoracic spine (n=9 with UFLUTS) and lumbar spine (n=6 with UFLUTS) regions (Table 6).

Common movement impairments observed in participants with UFLUTS

All participants with UFLUTS demonstrated a thoracic (P<.01) and hip (P=.02) movement impairment during at least one primary test (Table 6). The most common direction of movement impairments were thoracic flexion and hip adduction (Appendix 2).

Discussion

The results of this study suggest that a standardized examination consisting of traditional movement and positional tests and additional clinical tests may reveal movements and positions that provoke symptoms of UFLUTS. Correction of movement impairments identified during the standardized examination were effective at immediately reducing UFLUTS for some participants. Considering musculoskeletal impairment associations with UFLUTS may be important when determining management options for patients with UFLUTS. Physical therapists are uniquely qualified to address musculoskeletal impairments, movement, and postures, and should therefore be considered as a first line treatment provider in the behavioral management of patients with UFLTUS.

To our knowledge, only one previous study has been conducted to explore the relationship between musculoskeletal impairments of the low back, hip, pelvis and UFLUTS in the absence of urinary incontinence.[8] This is the first prospective study to indicate that movement impairments of the hip, spine, and pelvis may be associated with UFLUTS. Movement and positional testing including forward bend and return from forward bend, sidelying, and SLS may elicit movement impairments that provoke UFLUTS. Movement impairments that were most common and symptom-provoking among this cohort included thoracic flexion and hip adduction. Mechanical stresses applied to the thoracic spine and hip may be responsible for the increased UFLUTS experienced during these primary tests. Sympathetic innervation of the bladder originates from T10-L2 spine segments, and sensation of bladder filling is relayed from the bladder to spine segments T11-L2.[25] Prolonged or excessive movement into thoracic flexion during sustained postures and positions may increase tension on these nerves resulting in increased UFLUTS. Due to the attachments between the hip and pelvic floor muscles via the obturator internus muscle, it is possible that the position of the hip may impact UFLUTS. Patients with urinary urgency commonly posture into hip adduction.[26] Repetitive hip adduction may drive tissue changes such as trigger points to develop in the obturator internus muscle as it is lengthened in this position. Pelvic floor muscle trigger points are believed to contribute to symptoms of urinary urgency and frequency.[27,28]

Additional clinical tests commonly performed during a musculoskeletal examination to assess for hip and pelvic impairments were included in this study to identify possible associations between musculoskeletal impairments and UFLUTS. The pelvic girdle provides a stable platform for the spine and hip joint by absorbing forces from both the trunk and lower extremities. Over time, abnormal movement of the trunk or lower extremities may

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lead to increased stresses through the pelvis and hip joint. This can lead to pathology including pelvic girdle and hip joint pain or instability. The additional clinical tests included in this study are used to identify possible instability or asymmetry of the hip and pelvis. The results of these examination items can be used to determine appropriate rehabilitation strategies. Our cohort of participants with UFLUTS had more positive additional clinical tests compared to controls. This further supports the relationship between musculoskeletal connections of the hip and pelvis with urinary symptoms. Therefore, pubic symphysis palpation, FADIR, Stork testing, and hip IR should be considered during a musculoskeletal examination for patients with UFLUTS as these tests provoked urinary symptoms in some of our participants with UFLUTS.

Traditional physical therapy interventions for UFLUTS primarily focus on addressing impairments of the pelvic floor muscles.[4,5] Musculoskeletal impairments between the low back, hip, pelvis, and UFLUTS have now been shown in a large retrospective clinical chart review[8] and this prospective case-control study. This suggests that looking beyond the pelvic floor muscles at movements and postures of the spine, hip, and pelvis may be necessary to comprehensively address symptoms associated with UFLUTS.

Limitations of this study should be considered. The majority of our participants were under 50 years of age and nulliparous. Subjects reported relatively mild to moderate UFLUTS which may not represent a population of women who seek medical management for these symptoms. It was not possible to blind the clinical examiner to participant symptom status, but bias was minimized through the systematic examination procedures. The movement and additional clinical tests performed were chosen a priori and represent a subset of available tests. The results may not reflect the complete list of movement tests that may be considered as part of a standardized examination for patients with UFLUTS. Finally, this was a cross-sectional study, therefore, causal relationships between movement and symptoms cannot be made.

Conclusion

Movement and positional testing during a standardized physical therapy examination elicited movement impairments and provoked urinary urgency and frequency symptoms in participants presenting with UFLUTS. Correction of observed movement impairments immediately reduced UFLTUS symptoms for some participants. Additional clinical tests to assess for hip and pelvic girdle impairments also provoked UFLUTS. Inclusion of movement testing and tests to assess for hip and pelvic girdle impairments during a standardized physical therapy examination should be considered when evaluating patients with urinary urgency and frequency. Research is needed to illustrate treatment-based decision making following a standardized movement examination using the MSI approach for patients with UFLUTS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The study was approved by the Human Research Protection Office of Washington University in St. Louis (approval #201810086) and conducted in accordance with Declaration of Helsinki.

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TABLE 1

Inclusion and exclusion criteria for all participants with and without urgency and frequency predominant lower urinary tract symptoms (UFLUTS)

Inclusion Criteria	Exclusion Criteria
All	• Stress urinary incontinence or mixed incontinence more than once per month
• Women, ages 18–60	• Current or recurrent urinary tract infection[a] or gynecologic infection or cancer
• Able to speak and understand English	• Pelvic organ prolapse[a]
	• Previous surgery for prolapse or incontinence
Cases w/ UFLUTS	• Hip, pelvic, or trunk trauma or cancer
• Bothersome urgency or frequency in the past 4 weeks	• Abdominal or pelvic surgery in the past year
	• Current injury that would limit their ability to participate in testing
	• Onabotulinumtoxin injections to the bladder, pelvic floor or hip muscles
Controls	• Vulvovaginal dermatological conditions associated with UFLUTS
• No UFLUTS in the past 6 months	• Diabetes
	• Current pregnancy[a] or birth/termination/miscarriage in the past 12 weeks
• Age, BMI, & parity matched to cases	• Neurological involvement that would influence their coordination or balance
	• Implanted devices that impair the ability to visualize / make ultrasound measures[b]

[a] Items ruled out during final eligibility exam

[b] A separate study with the same participants called for ultrasound imaging[15]

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TABLE 2

Description of movement/positional tests and additional clinical tests

Test Name	Test Description	Participant Instructions
Forward bend	Active lumbar and hip flexion from standing position	“Bend forward like you are going to touch your toes”
Return from forward bend	Active return from lumbar and hip flexion in standing	“Come back up to standing”
Single-Leg stance[a]	Active hip and knee flexion of 1 limb to 90 ▫ hip flexion	“Stand on your (L) leg and lift your (R) thigh parallel with the floor”
Stork test[a,b,22]	Therapist palpated participant’s sacrum at S2 and PSIS while participant performed SLS	“Stand on your (L) leg and lift your (R) thigh parallel with the floor”
Sidelying position[a]	Preferred participant position in sidelying	“Lie down on your side however you are most comfortable”
Pubic symphysis palpation	Palpation of the anterior-superior border of the pubic symphysis in supine hook lying	
Seated passive hip IR[a,b]	Passive internal rotation of the hip with the hip and knee flexed to 90 ▫	“Let your foot hang heavy while I move your leg”
Seated passive hip ER[a,b]	Passive external rotation of the hip with the hip and knee flexed to 90 ▫	“Let your foot hang heavy while I move your leg”
FABER[a,b,23]	Passive hip flexion, abduction, and external rotation with knee bent in supine position, therapist applied downward overpressure at medial knee	“Let your leg hang heavy while I move it for you”
FADIR[a,b,23]	Passive hip flexion, adduction, internal rotation with knee bent in supine position, therapist applied overpressure in medial direction at lateral thigh	“Let your leg hang heavy while I move it for you”

[a]Tests were performed bilaterally.

[b]No correction was performed for this test.

[*]Palpating pressure was not quantified.

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TABLE 3

Criteria for determining positive additional clinical tests

Test	Positive Test
Stork test[22]	Cephalad motion of the PSIS relative to central S2
Hip ROM	Asymmetry in ROM between sides, or either side displays less than 45 degrees IR or ER
FADIR[23]	Pain in the anterior groin or hip
FABER[23]	Pain in the anterior groin or hip

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TABLE 4

Characteristics of women with and without urgency and frequency predominant lower urinary tract symptoms (UFLUTS)

Characteristic	UFLUTS (n=21)	Control (n=21)	Summary statistics (UFLUTS minus Control)	*P*
Age (years, mean ± SD [range])	28 ± 10 [19–56]	29 ± 9 [21–57]	−0.9 ± 3 [−5 – 4]	0.12[a]
BMI (kg/m^2, mean ± SD [range])	24 ± 4 [18–35]	25 ± 4 [19–33]	−0.4 ± 2 [−4 – 4]	0.40[a]
Vaginal parity (%)				
0	95	95		
2–3	5	5		
Race (%)				
Asian	19	5		
Black or African American	5	0		
White	76	81		
Other or Mixed-race	0	14		
Ethnicity (%)				
Hispanic or Latino	14	10		
Not Hispanic or Latino	86	90		
UCLA Activity Score (Median [IQR])	9 [5]	6 [5]	0.3 [3.6]	0.64
LUTS Tool (Median [IQR])				
LUTS Storage Symptom	9 [3]	1 [2]	7 [3]	<0.0001
LUTS Storage Bother	8 [4]	0 [0]	8 [5]	<0.0001
LUTS Voiding Symptom	6 [4]	0 [1]	5 [4]	<0.0001
LUTS Voiding Bother	2 [3]	0 [0]	2 [3]	<0.0001
Pelvic Floor Impact Questionnaire - 7 (median [IQR])				
PFIQ-7 Urogenital	24 [24]	0 [0]	24 [24]	<0.0001
PFIQ-7 Colorectal	0 [5]	0 [0]	0 [5]	0.004
PFIQ-7 Vagina/Pelvis	0 [5]	0 [0]	0 [5]	0.02

LUTS=Lower Urinary Tract Symptoms; SD=standard deviation; IQR=interquartile range defined as the 75th minus the 25th percentile.

[a] *P* value from two-tailed paired samples t-test (all others from two-tailed Wilcoxon signed rank)

The UCLA Activity Score is an ordinal self-report scale from 1 (No activity) to 10 (Regularly participates in high impact activity)

LUTS Tool scores were obtained by summing the frequency of LUTS (0–5) within each respective domain.

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TABLE 5

Number of participants with movement or positional impairments, urgency provoked with primary tests, and urgency relieved with secondary tests

	Participants Displaying an Impairment[a]			**Participants with Urgency Provoked with Primary Test[b]**			**Participants with Urgency Relieved with Secondary Test[c]**
Movement/Positional Test	**UFLUTS[f] n=21**	**Con[g] n=21**	**P[h]**	**UFLUTS[f] n=21**	**Con[g] n=21**	**P[h]**	**UFLUTS[f] n=21**
Forward bend	15	10	<.21	2	0	0.49	3
Return from forward bend	12	4	**0.03**	5	0	**0.05**	4
Single leg stance[e]	21	10	**<.01**	0	0	0.99	3
Sidelying[e]	21	12	**<.01**	3	1	0.61	11
	Participants Displaying a Positive Test[d]			**Participants with Urgency Provoked during Test[b]**			
Additional Clinical Tests[e]	**UFLUTS[f] n=21**	**Con[g] n=21**	**P[h]**	**UFLUTS[f] n=21**	**Con[g] n=21**	**P[h]**	
FADIR	7	4	0.48	8	1	**0.02**	
FABER	3	2	0.99	3	1	0.61	
Stork test	17	6	**<.01**				
Pubic symphysis palpation				16	5	**<.01**	
Hip ROM	17	12	0.18				
External Rotation ROM				2	0	0.50	
Internal Rotation ROM				5	0	**<.01**	

[a] Number of participants with any examiner-observed movement impairment in spine, pelvis or hip during primary test

[b] Number of participants who reported same or worse bladder urgency during primary test compared to baseline

[c] Number of participants who reported reduced bladder urgency with secondary test when compared to symptoms during the primary test

[d] Number of participants with positive test (see Table 4)

[e] Test performed bilaterally, participants only counted once regardless of if the phenomena occurred bilaterally

[f] Participants with bothersome urgency and/or day/night frequency at least sometimes in the past 4 weeks

[g] Participants without urgency and frequency symptoms

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[h] $p \leq .05$, values from Fisher's exact test

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TABLE 6

Frequencies of body region of movement and positional impairments observed

	Participants Displaying an Impairment During Primary Test[a]			Participants with Urgency Relieved with Secondary Test[b]
Region of impairment observed	**UFLUTS[c] n=21**	**Con[d] n=21**	**P[e]**	**UFLUTS[c] n=21**
Thoracic	21	14	**<0.01**	9
Lumbar	14	8	0.12	6
Hip	21	15	**0.02**	11

[a]Number of participants with any examiner-observed movement impairment in spine, pelvis or hip during primary test

[b]Number of participants who reported reduced bladder urgency with secondary test when compared to symptoms during the primary test

[c]Participants with bothersome urgency and/or day/night frequency at least sometimes in the past 4 weeks

[d]Participants without urgency and frequency symptoms

[e]P≤ .05, values from Fisher's exact test