Lower urinary tract symptoms in rheumatoid arthritis and spondyloarthritis male patients versus controls

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Background. We aimed to evaluate the severity of lower urinary tract symptoms (LUTS) in rheumatoid arthritis (RA) and spondyloarthritis (SpA) male patient versus control, then to determine the relation of LUTS with rheumatic diseases (RD) characteristics and with erectile dysfunction (ED).

Methods. We conducted a cross-sectional case control study including 50 men with RA or SpA and 50 healthy controls. LUTS were evaluated by the International Prostate Symptom Score (IPSS). LUTS bother was evaluated by the Quality of life (QoL) score, which ranges from 0 to 6. LUTS bother was considered if QoL score exceeded 2. Moreover, erectile function was assessed by the International Index of Erectile Function-5 (IIEF5) (ED if score < 21).

Results. LUTS were significantly more severe in RD patients than controls ($p = 0.03$). However, there was no difference between the two groups in LUTS bother (QoL) ($p = 0.2$). Comparing RA and SpA showed no difference as to the severity of LUTS or effect of bother on QoL ($p = 0.13$, $p = 0.5$). The prevalence of ED in RD patients was not significantly higher than controls (80% versus 70%; $p = 0.2$). There were also no differences either between RA and SpA groups ($p = 0.74$).

The severity of LUTS for patients with RD (RA and SpA) was significantly associated with age ($p = 0.001$), age at disease onset ($p = 0.002$) and ED ($p = 0.008$).

Conclusion. According to our study, men with RD seem to be exposed to more severe LUTS than controls. Also, the severity of LUTS was associated with ED, age of patients and the age of disease onset.

Key words: rheumatoid arthritis, spondylarthritis, lower urinary tract symptoms, erectile dysfunction, inflammation.

What is new? What is important?

- Lower urinary tract symptoms (LUTS) are significantly more severe in males with rheumatic diseases (RD)
- There is no difference between RD group and controls in the impact of LUTS on the quality of life (QoL)
- The prevalence of erectile dysfunction (ED) is not significantly more frequent in rheumatic disease (RD) patients than in controls
- The comparison of RA and SpA showed no difference in the severity of LUTS or in the impact of symptom bother on QoL

INTRODUCTION

Lower urinary tract symptoms (LUTS) are symptoms involving bladder, urinary sphincter, urethra and, in men, the prostate. LUTS may be caused not only by benign or malignant urological diseases but also by diseases entirely independent from urology like rheumatic diseases (RD) [1], systemic sclerosis [2] or Parkinson [3].

Spondyloarthritis (SpA) and rheumatoid arthritis (RA) are chronic rheumatic diseases, characterized by an inflammatory disorder that can lead to serious urogenital diseases with a high risk of urolithiasis, interstitial cystitis, bacterial urogenital infections and increased prevalence of erectile dysfunction (ED) in men [1]. However, LUTS problems are often ignored and few studies are reported about the influence of factors such as inflammation, disease

activity and treatments on the lower urinary tract of male patients with RA and SpA.

The first aim of this study was to evaluate the severity of lower urinary tract symptoms (LUTS) in RA and SpA male patient versus control and the second was to determine the relation of LUTS with RD characteristics and with ED.

MATERIAL AND METHODS

Study design

We conducted a cross-sectional case control study of 50 men with a RD in the form of RA according to the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria [4] or SpA fulfilling Assessment of Spondyloarthritis Society (ASAS) criteria [5]. The controls included 50 age-matched healthy men. Subjects were eligible for this study if they were sexually active. Patients were excluded if they were on drugs that can cause urinary symptoms or erectile problem, had anatomical defects of penis, had any neurological involvement, vascular disease (hypertension, heart disease, hyperlipidemia) or psychological disorders.

All subjects were informed and gave consent. The ethical committee of Mongi Slim Hospital gave the approval of the work in accordance to the national guidelines (number 20/19).

Data collection

For each patient and control, age, comorbidities (diabetes mellitus) and habits (smoking) were collected.

For RA and SpA patients, disease duration and age of diagnosis were collected. Disease activity was evaluated based on the level of erythrocyte sedimentation rate (ESR) (mm/H1) and C Reactive protein (CRP) (mg/l). It was also evaluated by the Disease Activity Score (DAS28 ESR) in RA patients [6]. In SpA patients, the disease activity was assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [7]. The Bath Ankylosing Spondylitis Functional (BASFI) was used to evaluate the functional disability in SpA patients [7].

Patients' treatments were assessed: non-steroidal anti-inflammatory drug (NSAIDs), conventional synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs) and biologic DMARDs (bDMARDs).

Assessment of lower urinary tract symptoms

The evaluation of urinary symptoms for male patients and controls was based on the International Prostate Symptom Score (IPSS), a validated questionnaire assessing disease severity. It is based on seven questions concerning urinary symptoms and one question concerning quality of life (QoL). Each of the seven questions included six answers indicating increasing severity of the urinary symptom. A score from zero to five is assigned to each answer. The total score can range from zero to thirty five (asymptomatic to very symptomatic). It categorizes symptoms as mild (score ≤ 7), moderate (score from 8 to 19) or severe (score from 20 to 35).

For the QoL question, also called "Bother question", it evaluates the impact of benign prostatic hyperplasia (BPH) symptoms on QoL. The answer ranges from delighted to terrible (0 to 6). LUTS bother was considered if the QoL question score exceeded 2.

Assessment of erectile function

The assessment of erectile function was based on the International Index of Erectile Function-5 (IIEF5). It is a self-reported questionnaire assessing the erectile function for the last six months.

The global score is obtained by adding the scores of five questions. It ranges from 5 to 25. The identification of ED is considered if the score was below 21.

Statistical analysis

Data were analyzed using SPSS software package version 11.5 and reported as means with standard deviations (SD), or as medians with interquartile ranges (IQR).

The Pearson Test was used for the correlation between two quantitative variables and the chi2 test between two qualitative variables. Student's test was used to compare between two means when the sample is normally distributed. Mann Whitney test was used to compare means of non-parametric data. The significance level was set at 0.05.

Linear logistic regression with "backward elimination" model was used to evaluate factors independently associated with the severity of LUTS. Significant factors ($p < 0.05$) and factors with p between 0.05 and 0.15 were included. Results were presented as beta coefficient (β) with a confidence interval (CI) of 95%.

RESULTS

A. Characteristics of patients and controls

No significant differences have been found between RD group and controls (Table 1) and also between RA and SpA patients (Table 2).

B. Rheumatic disease characteristics (SpA and RA)

Patients with RA had a mean disease duration of 7.1 ± 6.2 years and the age at disease onset was 42.9 ± 16.3 years. Mean disease activity was mild (DAS28 ESR = 2.28 ± 1.2). 84% of patients were on csDMARDs and 23% on bDMARDs.

Patients with SpA had a mean disease duration was 11.4 ± 7.1 years. Mean BASDAI, ASDAS CRP and BAFSI were respectively 2.5 ± 2.5 , 2.3 ± 1.05 and 2.5 ± 2.5 . Most of patients (90%) were on NSAIDs or csDMARDs and 56.7% were on bDMARDs.

There was no significant difference in inflammation parameters between RA and SpA groups: CRP ($p = 0.59$) and ESR ($p = 0.06$).

C. Evaluation of LUTS and LUTS QoL in patients with RD and controls

• Comparison of LUTS and LUTS QoL between RD patients and controls:

All patients accepted to complete the questionnaire. A significant difference was found

between the two groups in the severity of LUTS ($p = 0.03$), yet with no difference in LUTS QoL (bother question) ($p = 0.2$) (Table 3).

• Comparison of LUTS and LUTS QoL between RA and SpA patients

No significant differences appeared between RA and SpA groups either in the severity of LUTS, or in its impact on the QoL (Table 4).

D. Evaluation of the erectile function in patients with RD and controls

The prevalence of male ED in RD group was 80% versus 70% in controls ($p = 0.2$). Moreover, no significant differences between RA and SpA groups were found ($p = 0.74$).

E. Parameters associated with LUTS in males with RD

The comparison of patients according to the severity of LUTS in the RD population is illustrated in Table 5. There was a significant difference between the groups in patients' age, age at disease onset and ED (Table 5).

On linear regression analysis, only age and erectile dysfunction were independently associated with the severity of LUTS ($\beta = 0.3$, $p = 0.007$ and $\beta = -0.2$, $p = 0.06$ respectively).

Table 1

Characteristics of patients with RD and controls

Parameters	RD group (n = 50)	Controls (n = 50)	p
Age, mean $\pm$ SD	44.3 $\pm$ 12.1	48.8 $\pm$ 13.9	0.11
Diabetes mellitus, n (%)	4 (8)	14 (28)	0.09
Smoking, n (%)	20 (40)	29 (58)	0.714

RD: rheumatic disease, SD: standard deviation

Table 2

Comparison of characteristics of RA and SpA patients

Parameters	RA patients (n = 13)	SpA patients (n = 37)	p
Age, mean $\pm$ SD	49.6 $\pm$ 12.8	42.5 $\pm$ 11.4	0.06
Diabetes mellitus, n (%)	1 (17)	3 (8)	0.96
Smoking, n (%)	5 (38.4)	15 (40.5)	0.58

RA: rheumatoid arthritis, SpA: spondyloarthritis, SD: standard deviation

Table 3

Comparison of LUTS and LUTS QoL in patients with RD and controls

Parameters	RD group (n = 50)	Controls (n = 50)	p
Severity of LUTS			
-Mild, n (%)	32 (64)	38 (76)	0.03
-Moderate, n (%)	12 (24)	12 (24)	
-Severe, n (%)	6 (12)	0 (0)	
LUTS QoL (IPSS > 2)	12 (24)	7 (14)	0.2

RD: rheumatic disease, SD: standard deviation, LUTS: Lower urinary tract symptoms: QoL: quality of life

Table 4

Comparison of LUTS and LUTS QoL in patients with RA and SpA

Parameters	RA patients (n = 13)	SpA patients (n = 37)	p
Severity of LUTS			
– Mild, n (%)	8 (62)	24 (64.8)	0.3
– Moderate, n (%)	2 (15)	10 (27)	
– Severe, n (%)	3 (23)	3 (8.2)	
LUTS QoL (IPSS > 2) (n)	4 (30.7)	8 (21.6)	0.5

Significant at $p < 0.05$; SpA: spondylarthritis; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; IIEF: the International Index of Erectile Function, QoL: quality of life

Table 5

Parameters linked to the severity of LUTS in males with RD

	Mild LUTS (n = 32)	Moderate LUTS (n = 12)	Severe LUTS (n = 6)	p
Age (mean $\pm$ SD)	40.2 $\pm$ 11.5	48.6 $\pm$ 10.8	57.6 $\pm$ 10.8	0.001
Diabetes mellitus, n (%)	2 (11.1)	1 (8.3)	1 (16.6)	0.6
Smoking, n (%)	13 (40.6)	5 (41.6)	1 (16.6)	0.6
Age at disease onset (mean $\pm$ SD)	30.6 $\pm$ 12.2	40.4 $\pm$ 14.4	49.3 $\pm$ 9.5	0.004
Mean disease duration (years $\pm$ SD)	10.2 $\pm$ 6.8	11.7 $\pm$ 7.9	9.1 $\pm$ 6.9	0.78
Disease activity for SPA patients (n = 37)				
BASDAI (mean $\pm$ SD)	2.5 $\pm$ 1.8	3 $\pm$ 2.4	1.8 $\pm$ 1.7	0.8
ASDASCRP (mean $\pm$ SD)	2.2 $\pm$ 1	2.7 $\pm$ 1.2	2.5	0.4
Disease activity for RA patients (n = 13):				
DAS28ESR (mean $\pm$ SD)	3.1 $\pm$ 1.2	2.9 $\pm$ 0.5	1.54	0.2
CRP (mg/L) (mean $\pm$ SD)	16.7 $\pm$ 19.7	32.7 $\pm$ 35.1	3.7 $\pm$ 1.8	0.2
ESR (mm/H1) (mean $\pm$ SD)	29.7 $\pm$ 20.6	37.3 $\pm$ 35.3	20.5 $\pm$ 8.5	0.8
BASFI (mean $\pm$ SD)) for SPA patients (n = 37)	2.7 $\pm$ 2.6	2.9 $\pm$ 2.9	1.3 $\pm$ 0.3	0.6
NSAIDs, n (%)	11 (34.3)	3 (25)	3 (50)	0.6
csDMARDs, n (%)	16 (50)	7 (58.3)	3 (50)	0.1
bDMARDs, n (%)	14 (43.7)	8 (66.6)	2 (33.3)	0.18
Erectile function				
– Normal, n (%)	10 (31.2)	0 (0)	0 (0)	0.03
– ED, n (%)	22 (68.7)	12 (100)	6 (100)	

SPA: spondyloarthritis; RA: rheumatoid arthritis; LUTS: lower urinary tract symptoms; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease; ASDAS: Ankylosing Spondylitis Disease Activity Score, NSAIDs: non-steroidal anti-inflammatory drug; DMARD: disease modifying anti rheumatic drug; ESR: erythrocyte sedimentation rate, CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints.

Abbreviations:

- ED: erectile dysfunction
- RD: rheumatic disease
- RA: rheumatoid arthritis
- SA: spondyloarthritis
- ESR: erythrocyte sedimentation rate (mm)
- CRP: C Reactive protein (mg/l)
- DAS28: Disease Activity Score ESR (mm/1H)
- BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
- ASDAS CRP: Ankylosing Spondylitis Disease Activity Score
- BASFI: Bath Ankylosing Spondylitis Functional index
- NSAIDs: non-steroidal anti-inflammatory drug
- csDMARDs: conventional synthetic Disease Modifying Anti-Rheumatic Drugs
- bDMARDs: biologic DMARDs
- IIEF5: International index of erectile function-5

DISCUSSION

LUTS is a group of clinical symptoms involving bladder, urinary sphincter, urethra and, in men, the

prostate. Benign or malignant urological diseases may cause LUTS but also diseases that are entirely independent from urology such as inflammatory musculoskeletal diseases and systemic sclerosis [2].

Our study is the first to evaluate simultaneously the severity of LUTS in SpA and RA males, using a standard questionnaire (IPSS), and to compare it with controls.

In our study, the prevalence of moderate to severe LUTS in RD group and controls was respectively 36% and 24%. We found a significant difference in the severity of LUTS between RD groups and matched controls ($p = 0.02$). However, there was no difference between the two groups in the impact of LUTS on the QoL ($p = 0.2$). Likewise, according to a literature review of urological comorbidities in patients with RA, acute urinary retention is more common in chronic inflammatory musculoskeletal diseases like RA [1]. Some epidemiological studies have also shown that inflammatory rheumatic diseases are associated with increased risk of residual urine and acute urine retention (AUR) [8]. Moreover, a Finnish study by J. Koskima *et al.* found that arthritis was associated with LUTS [3]. However, in an Indian study, Dahak *et al.* observed that severe LUTS and LUTS QoL were not different between a SpA group and controls and that LUTS does not appear to be a significant issue [9]. Therefore, a routine assessment of urinary symptoms in SpA patients is not deemed necessary [9].

LUTS were reported in more frequently in woman with other rheumatic diseases, such as fibromyalgia (FM) and Systemic Lupus Erythematosus and Sjögren Syndrome (SS) but rarely in men with RA and SpA. De Carvalho Fusco *et al.* reported that women with FM had worse perineal function, frequent LUTS, and presented more urinary infections, which may impacts negatively on QoL [10]. Moreover, Jones *et al.* suggested that we should include the evaluation and treatment of urinary symptoms in FM management. Urinary symptoms seem to be associated with more severe FM symptoms [11]. Lee KL *et al.* reported similar urinary complaints between RA patients and controls [12]. However, those with secondary SS have a more sever LUTS. This finding is similar to the findings observed in patients with primary SS [12].

The reason for the association between RD and LUTS is unknown. The first explanation might be inflammation. H. Tarhan *et al.* demonstrated that inflammation (CRP level) was higher in patients with LUTS than controls. Besides, CRP levels significantly increased when frequency and urge incontinence scores are higher [13]. However, in our study, we did not find an association between inflammation

parameters (CRP and ESR) and the presence of LUTS.

Secondly, men suffering from RD are often over-medicated and this could suggest that LUTS is influenced by the use of immunomodulating drugs [1]. A systematic Review and Meta-Analysis of Randomized Controlled Trial proved that NSAIDs can improve urinary symptoms and flow measures [14]. However, in our study, NSAIDs, csDMARDs and bDMARDs were not associated with the severity of LUTS.

Thirdly, patients with RD are less able to go to the toilet and therefore may have more problematic urinary symptoms than men without RD [3].

In our study, the age of patients, the age of RD diagnosis and the ED significantly increased according to the severity of LUTS among men with RD, suggesting that decreased general health and late diagnosis have an impact on lower urinary tract function. Also, the severity of LUTS is possibly a factor of ED. In line with our study, results of several large-scale studies have shown a significant association between LUTS and ED. A study of 2,476 Spanish men aged from 25 to 70 years with a prevalence of ED between 12% and 19%, indicated LUTS and RD as risk factors for ED [15].

Moreover, data from the National Health and Social Life Survey (NHSLs) of adults aged from 18 to 59 years indicated that LUTS was a significant predictor for ED [16]. Furthermore, Rosen *et al.* demonstrated that men with moderate-to-severe LUTS in patients with benign prostatic hyperplasia (BPH) have a higher risk for sexual dysfunction, ejaculatory dysfunction, and hypoactive desire. It appears that the mechanisms of LUTS may have an impact on both the erection and ejaculation components of the sexual activity [17].

In another study, a covariance analysis controlling for age and other comorbidities showed that LUTS severity, as determined by IPSS score, was a highly significant predictor of all IIEF domain scores: Erectile function ($R = 0.214$; $p < 0.001$), intercourse satisfaction ($R = 0.120$; $p < 0.001$), orgasmic function ($R = 0.187$; $p < 0.001$), sexual desire ($R = 0.149$; $p < 0.001$), and overall satisfaction ($R = 0.138$; $p < 0.001$) [18].

Concerning the ED, only few studies with a limited number of participants were made in SpA and RA male patients. In our study, there was no significant difference between the RD group and controls in ED prevalence. However, Pirildar *et al.* reported in a study of 65 SpA male patients that

erectile function was the most affected domain [19].

More importantly, no comparative study between SpA and RA on LUTS and erectile function was found in literature. In our study, there was no difference between the RA and SpA groups in LUTS severity, presence of LUTS bother and ED prevalence.

It should be noted that our study has some limitations given its monocentric nature with a limited sample size. The results can therefore not be generalized to the rest of the population. Another limitation is the lack of urogenital examination, ultrasonography exploration and urodynamic evaluation. Moreover, we did not exclude smoker

and diabetics. However, both rheumatic disease group and control group were similar concerning diabetes and smoking. Besides, these parameters were not significantly associated with LUTS.

CONCLUSIONS

In the light of the present study, LUTS seems to be more severe in men with RD than in the general population. It is also associated with patient's age, age at disease onset and ED. Future longitudinal studies are needed to observe the effect of RD on urinary symptoms and erectile function.

Introducere. Scopul studiului a fost de a evalua severitatea simptomelor tractului urinar inferior (LUTS) la pacienții de sex masculin cu artrită reumatoidă (RA) și spodilartropatii (SpA), comparativ cu un lot martor și de a determina relația LUTS cu caracteristicile bolii reumatice și disfuncția erectilă.

Metode. A fost realizat un studiu transversal ce a inclus 50 de pacienți cu RA sau SpA și 50 de martori sănătoși. LUTS au fost evaluate folosind un scor – International Prostate Symptom Score (IPSS). A fost evaluată și calitatea vieții (QoL). Disfuncția erectilă (ED) a fost evaluată folosind International Index of Erectile Function-5 (IIEF5). Pentru un scor sub 21 s-a pus diagnosticul de ED.

Discutii. LUTS au fost mai severe la pacienții cu patologie reumatică, comparativ cu martorii. Nu au fost diferențe între cele două grupuri referitor la afectarea QoL. Comparativ, între RA și Sp nu au fost diferențe semnificative privind afectarea QoL. Prevalența ED a fost similară la pacienții cu boli reumatismale și martorii sănătoși. Similar, nu au existat diferențe privind prevalența ED la pacienții din grupul RA și SpA. Severitatea LUTS la pacienții cu RA și SpA s-a asociat cu vârsta ($p = 0,001$), vârsta de debut a patologiei reumatice ($p = 0,002$) și ED ($p = 0,008$).

Concluzii. Pacienții cu boli reumatice par să fie expuși la LUTS mai severe decât martorii sănătoși. Severitatea LUTS s-a asociat cu ED, vârsta pacienților și vârsta de debut a patologiei reumatice.

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Funding: This research received no grant from any funding agency in the public, commercial or non-profit sectors.

Conflict of interest disclosure: None declared.

Ethics approval: The local committee approved the study before any data were collected. All applicable national guidelines were followed (number 20/19).

Consent to participate: Informed consent was obtained from all participants included in the study.

Availability of data and material: Data and material are available.

Acknowledgments: We thank the department of rheumatology and urology for assistance.

Author contribution statement: All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Received 1st August 2020