Physical Activity as a Protective Factor for Lower Urinary Tract Symptoms in Male Patients: A Prospective Cohort Analysis

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OBJECTIVE To assess the association between physical activity, evaluated by the Physical Activity Scale for Elderly (PASE) questionnaire and lower urinary tract symptoms (LUTS) in male patients.

METHODS From 2009 onward, a consecutive series of patients with LUTS-benign prostatic enlargement were enrolled. Symptoms were evaluated using the International Prostate Symptom Score (IPSS) with its subscores and prostate volume using transrectal ultrasound. Physical activity was evaluated with the PASE questionnaire, consisting of 12 questions regarding frequency and duration of leisure activity and recently used to evaluate physical activity in patients with prostatic disorders. The risk of detecting LUTS (IPSS ≥8), voiding LUTS (vIPSS≥5), and storage LUTS (sLUTS) (sIPSS ≥4) was evaluated using binary logistic regression analysis.

RESULTS Six hundred and seventeen patients were enrolled in 2 centers (Rome, Vasto, Italy). Median PASE score was 118 (IQR 73/169), and median IPSS was 9 (IQR 5/15). Overall 189 of 617 (30%) patients presented moderate/severe LUTS. These patients presented a lower PASE score (111 IQR 69/160 vs 125 IQR 83/180; $P = .016$) when compared to patients with total IPSS ≤7.

On multivariate analysis, PASE score (OR = 0.997 per unit, 95%CI: 0.994-1.000; $P = .023$), and prostate volume (OR = 1.008 per mL, 1.000-1.016; $P = .045$) were independent predictors of LUTS severity. As well PASE score was an independent predictor of moderate/severe sLUTS (OR = 0.996, 95%CI:0.993-0.999; $P = .015$).

CONCLUSION In our study a reduced physical activity, assessed using the PASE questionnaire, is associated with an increased risk of moderate severe LUTS, more specifically of moderate/severe sLUTS. UROLOGY 125: 163–168, 2019. © 2019 Elsevier Inc.

Lower urinary tract symptoms (LUTS) represent a highly prevalent condition in male patients, rising progressively with age.[1,2] Several urological and nonurological conditions can contribute to the onset and progression of LUTS. Benign prostatic obstruction, secondary to benign prostatic enlargement (BPE) represents one of the main underlying causes in male patients.[1,3]

The pathophysiology of Benign Prostatic Hyperplasia (BPH) is still unknown. Several studies have evaluated the role of hormones and genetic predisposition. As well, other studies have assessed the role of modifiable risk factors such as cardiovascular diseases, obesity, diabetes, dyslipidaemia, and the metabolic syndrome in LUTS/BPH pathogenesis. Recently, some authors have explored the possible role of physical activity in LUTS/BPH pathogenesis. Exercises protect against cardiovascular disease and indeed increasing physical activity has been associated with decreased risk of BPH surgery, clinical BPH, histological BPH, and LUTS.[3,4] However, the association

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between LUTS/BPH and physical activity is still a matter of debate.

The heterogeneity in study population, exercise intensity, study design, and findings do not allow definitive conclusions. One important limitation of the available evidence is the lack of a standardized definition and methodology in the evaluation of physical activity. The Physical Activity Scale for Elderly (PASE) questionnaire was initially developed in the early 90s to provide an instrument to investigate older people's physical activity with an age-specific questionnaire, filling what was an important need in epidemiologic research at that time. PASE questionnaire is a practical and widely used approach for physical activity assessment in epidemiologic investigations.[5] It is a brief (5 minutes) and easily scored survey designed specifically to assess physical activity in elderly patients.[5] The PASE score includes information on leisure, household, and occupational activity.[6] In the literature, PASE questionnaire has been widely validated to assess physical activity in many diseases. In urology, PASE questionnaire showed excellent properties in evaluating physical activity in patients with prostate cancer.[7]

With this knowledge in mind, aim of our study was to assess the association between physical activity, evaluated by the PASE questionnaire and LUTS in male patients.

METHODS

From January 2009 to September 2013 each new male patient, aged 50 years or older with LUTS, presenting at our outpatient clinic, was prospectively enrolled. The study was approved by the local ethical committees, all patients signed a dedicated informed consent and the study was conducted in accordance with the principles of the declaration of Helsinki.

Exclusion criteria were: patients with neurological disorders, renal insufficiency, bladder stones, prostate cancer, urethral stricture, previous pelvic surgery, urinary infections, currently on alpha-blockers or 5-alpha-reductase inhibitors, or with a prostate volume ≤ 30mL. Patients with a Prostate Specific Antigen (PSA) level ≤ 4 ng/mL and/or a positive digital rectal examination were excluded or addressed to a prostatic biopsy.

Patients underwent a detailed medical history and physical examination. Physical examination included digital rectal examination, waist circumference, height, weight, and blood pressure measurement. Body mass index (BMI) was calculated as weight/height^2. All patients underwent a transrectal ultrasound to assess their prostate volume using a Falcon ultrasound equipment (B-K Medical, Milan, Italy) equipped with a 5-10 MHz bi-convex probe (8808 probe B-K Medical, Milan, Italy). Prostate volume was then calculated using the ellipsoid formula.

LUTS were assessed using the International Prostatic Symptom Score (IPSS).

The IPSS voiding (vIPSS, Questions No 1-3-5-6) and storage subscores (sIPSS, Questions No 2-4-7) were separately calculated. Thus, moderate/severe LUTS were defined as total IPSS ≥8,[1,2] moderate/severe storage LUTS (sLUTS)as sIPSS ≥4, and moderate/severe voiding LUTS as vIPSS ≥5.[8]

Physical activity was evaluated with the PASE questionnaire.[5] The PASE questionnaire includes different items about occupational, household, and leisure activities. It consists of 12 questions on the frequency and duration of leisure activity (eg, sports, jogging, swimming, strengthening, and endurance exercise), household activity and work-related activity. Participation in leisure-time and strengthening activities are scored as "never," "seldom" (1-2 d/wk), "sometimes" (3-4 d/wk), and "often" (5-7 d/wk). Duration of these activities is scored as <1, 1-2, 2-4, and >4 hours. Household and work-related activities are scored as "yes" or "no". In work-related activities, paid or unpaid work is scored in h/wk. The total PASE score is computed by multiplying either the time spent in each activity (h/wk) or participation (ie, "yes"/"no") in an activity, by empirically derived item weights and then summing overall activities. The overall PASE score ranges from 0 to 400 or more. Therefore, a patient walking 1 hour for 3 d/wk reaches a PASE score of 15 for this item. The total PASE score of this patient is obtained by summing the different subscores obtained for each of the items.[5] The PASE questionnaire was given to all the patients and they were instructed to complete the questionnaire at home at their convenience and return it in a provided, preaddressed stamped envelope. Patients stating that their actual physical activity status has significantly changed over the last 5 years were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the S-PSS 12.0 (SPSS Inc, Chicago, IL) software. Evaluation of data distribution using the Kolmogorov-Smirnov test showed a non-normal distribution of the study data set. As proposed in the Boston area Community Health Survey, IPSS was both considered as continuous variable and categorical one dividing patients in mild symptoms (IPSS: less than 8) versus moderate or severe symptoms (IPSS: 8 or greater).[9] Symptoms were further categorized as voiding and storage and dichotomized as 5 or greater versus less than 5 for voiding and 4 or greater versus less than 4 for storage.[9-11] Univariate analysis was performed with the chi square test for categorical variables and using the Kruskall-Wallis 1-way analysis for continuous variables. The risk of moderate/severe LUTS (IPSS ≥8), moderate/severe sLUTS (sIPSS ≥4), and moderate/severe voiding LUTS (vIPSS ≥5) was assessed using binary logistic regression analysis.[2,9-11] An alpha value of 5% was considered as the threshold for significance. Data are presented as median (range), mean ± standard deviation.

RESULTS

Six hundred and seventeen patients were enrolled in 2 centers of Italy, Rome, and Vasto. Overall characteristics of the cohort are reported on Table 1.

Patient's characteristics according to LUTS severity are reported in Table 1. Overall 189 of 617 (30%) patients presented moderate/severe LUTS (IPSS ≥8). Overall, 30 of 617 (5%) patients presented Diabetes Mellitus (DM) and 10 of 30 (33%) presented moderate severe LUTS ($P > .05$). Patients with moderate/severe LUTS presented no difference in terms of age, BMI, waist, and PSA values when compared to patients with mild LUTS (IPSS ≤7). However, patients with moderate/severe LUTS presented higher prostate volumes (54 IQR 33/80 vs 48 IQR 35/63; $P = .046$) and a lower PASE score (111 IQR 69/160 vs 125 IQR 83/180; $P = .016$) when compared to patients with mild LUTS.

On age-adjusted multivariable analysis, PASE score (OR: 0.997, CI: 0.994-1.000; $P = .023$) and prostate volume (OR: 1.008, CI: 1.000-1.016; $P = .046$) were independent predictors

Table 1. Patient's characteristic overall and according to IPSS severity.

	Overall	IPSS ≤ 7 (428 Patients)	IPSS ≥ 8 (189 Patients)	*P Value
Age (y)	66.95 ± 7.97; 67 (61/73)	66 ± 7; 67 (61/73)	67 ± 6; 68 (62/73)	0.306
PSA (ng/mL)	7.68 ± 4.42; 6.65 (4.8/9.2)	7.2 ± 3; 6.65 (4.9/9)	6.2 ± 3; 6.65 (4.8/9.8)	0.367
BMI (Kg/m^2)	26.80 ± 3.57; 26 (24.5/28.7)	26.1 ± 3; 26.44 (24.3/28.7)	26.3 ± 3; 26.42 (24.7/28.6)	0.998
Waist (cm)	101.9 ± 9.56; 101 (96/108)	101 ± 8; 101 (95.75/108)	102 ± 8; 102 (97/107)	0.497
PASE	128 ± 80.54; 118 (73/169)	126 ± 60; 125 (83/179)	110 ± 63; 111 (69/159)	0.016
TRUS (cc)	55 ± 28.3; 50 (35/69)	47 ± 25; 48.5 (35.8/63)	52 ± 27; 54 (33/80)	0.046
IPSS voiding	5.76 ± 4.5; 5 (2/8)	2.56 ± 3.2; 3 (1/5)	8.34 ± 3.5; 8 (5/12)	0.001
IPSS storage	4.65 ± 3.25; 4 (2/7)	2.3 ± 1.5; 2 (1/5)	7.85 ± 4.5; 5 (2/8)	0.001
IPSS total	10 ± 6.65; 9 (5/15)	5.45 ± 4.5; 5 (2/8)	15.45 ± 4.5; 15 (10/20)	0.001

IPSS, International Prostate Symptom Score; PASE, physical activity scale for elderly.
Data are presented as mean ± DS; median (IQR).

of LUTS severity. More specifically patients with a reduced physical activity and large prostates were at an increased risk of moderate/severe LUTS.

In a separate analysis of voiding and storage sub-scores of the IPSS questionnaire, patients with moderate/severe sLUTS presented a lower PASE score when compared to patients with mild sLUTS. Although patients with moderate/severe voiding LUTS presented lower PASE scores when compared to patients with mild voiding LUTS, the difference was not statistically significant ($P = .061$). On multivariate analysis age and PASE were predictors of sLUTS risk while only prostate volume was a predictor of voiding LUTS (Table 2).

DISCUSSION

The present study evaluates the association between physical activity and LUTS severity in male patients. According to our experience, poor physical activity evaluated by the PASE questionnaires represents a risk factor for moderate/severe LUTS (IPSS ≥8). More specifically reduced physical activity increased the risk of sLUTS. Moreover, as already widely demonstrated by the available literature,[4,10] we confirm that patients with larger prostates are more symptomatic. Clearly, our findings confirm the available evidence on the relationship between LUTS and physical activity.[12]

Several studies have evaluated the relationship between physical activity and LUTS due to BPE, however only few of them have used the PASE questionnaire introduced by Washburn and Montoye 1993.[13] Parsons et al evaluated the association between LUTS and physical activity in a group of elderly over-weighted (BMI: 25.0-29.9 kg/m^2) and obese (30 kg/m^2) patients. Physical activity was self-reported using 2 assessments: first, participants provided a detailed assessment of their household, leisure, and occupational activities in the past 7 days on the 12-item PASE; second, participants were asked, "Do you take walks for exercise, daily or almost every day? (yes or no)." According to their results, over-weighted and obese patients were 29% (adjusted odds ratio: 1.29; 95% CI 1.00-1.68) and 41% (OR: 1.41; 95% CI, 1.03-1.93) more likely to develop LUTS, respectively.[14] Moreover, in older men, modest amounts of physical activity and walking appear to be associated with a reduction in the 5-years incidence of LUTS.[14] In 1998, Platz et al investigated in a prospective study age, race or ethnicity, alcohol consumption and smoking, and physical activity demonstrating that was inversely related with BPH (extreme

Table 2. Multivariate binary logistic regression for the risk of LUTS (IPSS ≥8), for the risk of storage LUTS (sLUTS) and voiding LUTS (vLUTS).

	Risk of LUTS (IPSS ≥8)			Risk of sLUTS			Risk of vLUTS		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age (y)	1.014	0.988-1.041	0.291	1.031	1.005-1.059	0.021	0.994	0.969-1.021	0.670
PASE	0.997	0.994-1.000	0.023	0.996	0.993-0.999	0.015	0.997	0.994-1.000	0.061
TRUS	1.008	1.000-1.016	0.046	1.001	0.993-1.008	0.840	1.009	1.001-1.016	0.022

PASE, physical activity scale for elderly.

quintiles: OR, 0.75; 95% CI, 0.67-0.85; P for trend, <.001), surgery for BPH (OR, 0.76; 95% CI, 0.64-0.90; *P* for trend, <.001), and symptomatic BPH (OR, 0.75; 95% CI, 0.64-0.87; *P* for trend, <.001). Walking, the most prevalent activity, was inversely related to BPH risk; men who walked 2-3 h/wk had a 25% lower risk of BPH. They concluded that physically active men have a lower frequency of LUTS. They supposed that, a reduction in systemic sympathetic nervous system activity at rest resulting from sustained physical activity could also reduce prostatic smooth muscle tone thus mitigating the severity of LUTS.[15] In a systematic review and meta-analysis of observational studies, Parsons et al evaluated the association of physical activity with BPH and LUTS.[16] Eleven (*n* = 43,083 men) studies were included with the following results. Eight studies observed inverse, 2 studies null, and 1 study equivocal associations of physical activity with BPH or LUTS. Eight studies (*n* = 35,675) were eligible for pooled analyses. They stratified physical activity levels into light, moderate, and vigorous categories, with a sedentary category for reference. Compared to the sedentary group, the pooled odds ratios for BPH or LUTS were 0.70 (95% CI 0.44-1.13, *P* = .14), 0.74 (95% CI 0.60-0.92, *P* = .005), and 0.74 (95% CI 0.59-0.92, *P* = .006) for men engaging in light, moderate, and heavy physical activity, respectively. They concluded that physical activity reduces the risks of BPH and LUTS.

Although the exact pathophysiology behind this association is still unknown: inflammation[12,16] and the metabolic syndrome may play a role[17-23] and could probably support our different results on the relationship between PASE score with storage rather than voiding LUTS. Particularly most of the studies on the relationship between inflammation, MetS, and LUTS supported a more significant effect of these 2 conditions on storage symptoms.[24,25]

Regarding the possible role of inflammation in the association between physical activity and BPH, chronic exercise is a strong inductor of endogenous antioxidant protection pathways[26]; it stimulates innate immune function and surveillance, and it leads to decreases in systemic inflammation and proinflammatory factors.[27] Moreover aerobic exercise may influence serum levels of sex steroid hormones,[28] which can be involved in prostate hyperplasia and cancer pathogenesis.[24,27] Poor diet and reduced physical activity are the main causes of MetS which has been also recently considered as a risk factor for LUTS related to BPE or overactive bladder through different mechanisms including the development of inflammatory infiltrates into the prostate, pelvic atherosclerosis, and increased autonomic nervous system activity.[29] Patients with MetS present higher inflammatory score when compared with patients with no metabolic factors.[30,31] As well, some evidence suggest that an increase in autonomic nervous system activity, as observed in patients with MetS, may contribute to detrusor muscle contraction and consequently to detrusor overactivity.

As well, Nunzio et al observed possible association between metabolic syndrome and prostate inflammation in an observational study. In a consecutive series of patient treated with transurethral resection of the prostate, patients with MetS presented a higher proportion of inflammatory infiltrates when compared to patients without MetS (45 of 54; [83%] vs 52 of 77; [67%], *P* = .01).

We must also acknowledge some important limitations of our study. We have no data on uroflow and postvoid residual volume as well as no dedicated questionnaires were used to exclude or better evaluate patients with overactive syndrome, or to investigate all the possible conditions behind male LUTS. We have no data on the smoking status of our patients and only a small number of patients (30 of 617:[5%]), in line with diabetes prevalence in our outpatient LUTS population,[32] presented diabetes. As recently showed by our group patients with moderate/severe cardiovascular risk (including smoking and diabetes) presented a higher risk of sLUTS and particularly of nocturia.[33] The lack of these significant data represents an important limitation for our study, however we must underline that our study mostly focused on physical activity which is considered one of the main drivers of metabolic factors including diabetes. Furthermore, even if it is a 2-centre study, our study has a limited population of patients with just 617 patients. Our results clearly depend on the enrolled population (male patients with LUTS and a prostate volume ≥30 g) and cannot be extended to all patients with LUTS. We have performed the study in a southern European cohort of patients that may be different from racially diverse Northern European, Northern American, Southern American, and Asian populations. Our present cohort characteristics describe an Italian population that is certainly representative of our geographical region. The study also presents some biases, which are typical of all the available physical activity methods or questionnaires.[34] Physical activity reported may not reproduce physical activity earlier in life and furthermore any protective effect of exercise may require lifelong exposure. Consequently, the relevance of a single measurement at a given point in time depends on the degree to which exposure tracks over time. To minimise these factors, we included in the study exclusively patients reporting no changes in their physical activity status over last years. There is also a possibility that health-conscious men, who spend more time on physical activity, lead a healthier lifestyle, with a reduced intake of dietary fat and meat, other possible risk factors for LUTS and BPH. Therefore, it can be difficult to determine how these potential risk factors have a role in our present results.

Surely our results represent a further contribution in the evaluation of the possible influence of the environmental factors in the development of LUTS. Although no definite conclusions can yet be drawn, the hypothesis of a relationship between reduced exercise and LUTS remains an interesting area for research. We strongly support that evaluation of the physical activity status, as well as obesity and metabolic factors, as proposed by several authors[12,35] should be part of the routine assessment of patients with prostatic disease including patients with LUTS. The

possibility of influencing prostate diseases and LUTS development by acting upon patients' physical exercise levels has been also proposed as a promising area of clinical research. The implementation of the PASE questionnaire in urological practice represents a further area of research in the future years.

However, at present, this represents the first prospective series in Europe evaluating the association between physical activity evaluated by PASE questionnaire, defined using standard criteria, and LUTS using I-PSS in patients with BPE.

Our results, if confirmed in other experiences, could highlight the importance to evaluate and identify physical activity status in urological patients. It will be reasonable to suggest that our patients exercise regularly, eat a balanced diet, and maintain a healthy weight in order to probably improve their LUTS but definitively their health.

CONCLUSION

We observed that a reduced physical activity, assessed using the PASE questionnaire, is associated with an increased risk of moderate severe LUTS in an Italian population. Further studies in larger patient population across multiple institutions and countries are needed to confirm our results, to better understand the molecular pathways behind this association and to evaluate the possible impact of physical activity on LUTS/BPE development and progression.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.12.035.

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