Interactions between Lower Urinary Tract Symptoms and Cardiovascular Risk Factors Determine Distinct Patterns of Erectile Dysfunction: A Latent Class Analysis

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Purpose: An epidemiological association between lower urinary tract symptoms and erectile dysfunction is well established. However, interactions among multiple risk factors and the role of each in pathological mechanisms are not fully elucidated

Materials and Methods: We enrolled 898 men undergoing prostate cancer screening for evaluation with the International Prostate Symptom Score (I-PSS) and simplified International Index of Erectile Function-5 (IIEF-5) questionnaires. Age, race, hypertension, diabetes, dyslipidemia, metabolic syndrome, cardiovascular disease, serum hormones and anthropometric parameters were also evaluated. Risk factors for erectile dysfunction were identified by logistic regression. The 333 men with at least mild to moderate erectile dysfunction (IIEF 16 or less) were included in a latent class model to identify relationships across erectile dysfunction risk factors.

Results: Age, hypertension, diabetes, lower urinary tract symptoms and cardiovascular event were independent predictors of erectile dysfunction ($p < 0.05$). We identified 3 latent classes of patients with erectile dysfunction (R^2 entropy = 0.82). Latent class 1 had younger men at low cardiovascular risk and a moderate/high prevalence of lower urinary tract symptoms. Latent class 2 had the oldest patients at moderate cardiovascular risk with an increased prevalence of lower urinary tract symptoms. Latent class 3 had men of intermediate age with the highest prevalence of cardiovascular risk factors and lower urinary tract symptoms. Erectile dysfunction severity and lower urinary tract symptoms increased from latent class 1 to 3.

Conclusions: Risk factor interactions determined different severities of lower urinary tract symptoms and erectile dysfunction. The effect of lower urinary tract symptoms and cardiovascular risk outweighed that of age. While in the youngest patients lower urinary tract symptoms acted as a single risk factor for erectile dysfunction, the contribution of vascular disease resulted in significantly more severe dysfunction. Applying a risk factor interaction model to prospective trials could reveal distinct classes of drug responses and help define optimal treatment strategies for specific groups.

Key Words: penis, erectile dysfunction, lower urinary tract symptoms, age groups, risk

Abbreviations and Acronyms

AIC = Akaike information criterion

BIC = Bayesian information criterion

BMI = body mass index

ED = erectile dysfunction

LC = latent class

LCA = latent class analysis

LCM = latent class model

LUTS = lower urinary tract symptoms

NO = nitric oxide

PDE5-I = phosphodiesterase 5 inhibitor

WHR = waist-to-hip ratio

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Erectile dysfunction and LUTS are highly prevalent conditions in older men that cause significant quality of life impairment.[1,2] Solid evidence demonstrates an association between LUTS and ED.[3] Although many risk factors are common to the 2 conditions, such as cardiovascular disease and diabetes mellitus, many well designed, community based studies show an independent association between LUTS and ED.[4–6] Evidence from clinical trials and experimental studies contribute to the understanding of this association. The hypothesized mechanisms of interaction are decreased NO, alteration in the Rho-kinase pathway, autonomic hyperactivity, pelvic atherosclerosis and sex hormone imbalance.[3,7,8] However, elucidating the underlying mechanisms is challenging since many pathways are interrelated with other risk factors, such as dyslipidemia and hypertension.[9,10] Although to date epidemiological studies have shown a persistent association after adjustment for multiple variables, they have not fully elucidated how LUTS and cardiovascular risk interact and the relative role of each in ED pathogenesis.

The relationship between LUTS and ED has gained attention after randomized trials revealed that PDE5-I used for ED could be efficacious in decreasing LUTS secondary to benign prostatic hyperplasia.[11,12] There remains a significant rate of treatment failure and the advantage of the association of α1-adrenergic blockers is still not clear. Further understanding of the role of risk factors and their relation to mechanisms causing LUTS and ED may help determine which patient groups could benefit from PDE5-I monotherapy or combination therapy. We investigated interactions of risk factors and their relative impact on ED severity using LCA.

MATERIALS AND METHODS

Institutional review board approval was obtained before beginning the investigation. All men undergoing prostate cancer screening at a single institution in 2012 were enrolled in the study. Screening was indicated for all men at age 50 years or greater. Patients diagnosed with prostate cancer were excluded from analysis. Other exclusion criteria were previous prostate or bladder cancer, spinal cord injury, history of pelvic surgery or radiotherapy and current use of 5α-reductase inhibitors, α-blockers or PDE5-I.

Data were collected on a structured data sheet by a urologist from the research staff. Evaluation included age, medications, urological conditions and comorbidities such as hypertension (blood pressure 130/85 mm Hg or greater, or antihypertensive drug use), diabetes mellitus (fasting plasma glucose 100 mg/dl or greater, or diabetes drug use), dyslipidemia (serum high density lipoprotein less than 40 mg/dl, triglycerides 150 mg/dl or greater, or lipid medication use) and previous cardiovascular events. BMI was recorded, as was waist and hip circumference. Obesity was defined as BMI 30 kg/m^2 or greater. Cutoffs for waist circumference and WHR were 102 cm and 1, respectively. Metabolic syndrome was defined as at least 3 of 5 defining criteria, including hypertension, low high density lipoprotein, and increased plasma glucose, triglycerides and waist circumference.[13]

Patients underwent digital rectal examination and serum prostate specific antigen evaluation for prostate cancer screening. Serum hormone evaluation included free and total testosterone, luteinizing hormone and follicle-stimulating hormone.

Assessments

Erectile dysfunction. We assessed ED using the simplified IIEF-5.[14] Subjects were classified with no ED—score 22 to 25, or mild—17 to 21, mild to moderate—12 to 16, moderate—8 to 11 or severe ED—5 to 7. Men with mild or no ED (score 17 to 25) were compared to those with moderate to severe ED (score 5 to 16).

Lower urinary tract symptoms. We evaluated LUTS with the I-PSS. Subjects were divided into groups with no or mild—0 to 7, moderate—8 to 19 and severe LUTS symptoms—20 to 35. Men with moderate/severe symptoms were further compared to those with mild or no LUTS. Moderate/severe voiding symptoms were defined as a sum of 4 or greater on I-PSS questions on intermittence (question 3), weak stream (question 5) and straining (question 6).[15] Storage symptoms were defined as a sum of 4 or greater for frequency (question 2), urgency (question 4) and nocturia (question 7).

Statistical Analysis

Univariate analysis of ED predictors was performed as a first evaluation of the sample for comparison to other populations. The Pearson chi-square test was used to compare categorical variables. Significant factors were further analyzed in a logistic regression model.

LCA is a multivariate statistical approach that describes relationships among a set of observed variables. It groups individuals with similar patterns of response to measurements to obtain more uniform, meaningful classes in a heterogeneous population.[16] LCA generates predicted probabilities of the response to each variable for each LC. Each subject is assigned to a class by the highest class membership probability among the classes.

This method was initially developed in psychiatry and related fields in which the relationship among known risk factors for a given outcome was studied.[17] LCA has recently found significant applications in many other clinical situations, such as identifying daytime wetting patterns,[18] graft dysfunction after lung transplantation[19] and physical activity practice.[20]

We used a LCM to identify how risk factors interact and their impact on ED severity. Variables independently associated with ED on logistic regression were included in the model. A panel of specialists revised the variables included among the data collected for univariate analysis. To help determine the number of classes for the model with the best fit we used the AIC and BIC.[21] Factors associated with LCs were analyzed and compared with